The 'oRAcle' Study – identifying predictors of adverse outcomes in Rheumatoid Arthritis

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The ‘oRAcle’ Study – Identifying Predictors of Adverse Outcomes in Rheumatoid Arthritis

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Abstract

Introduction

Rheumatoid Arthritis (RA) is an immune mediated inflammatory joint disease, primarily affecting synovial tissue leading to joint damage and physical disability. The disease affects over half a million people in the UK. Over the last 50 years, outcomes in RA have dramatically improved with the advent of immune modulatory therapy. Despite improvements in our knowledge of its immunopathology and a huge armamentarium of effective treatments, patients continue to succumb to clinically important adverse outcomes. The adverse outcomes that are the focus of this thesis are based on the following specific themes: (1) disease flare (2) treatment non-response and (3) treatment related adverse events.

Methods

A range of epidemiological methods and techniques have been applied to the investigation of adverse outcomes in RA. This includes quantitative analyses of clinical trial data from the REMIRA (REMission in RA) cohort and the OPTTIRA (optimizing treatment with TNF inhibitors in RA study) cohort examining disease flare, and observational data from the BSRBR-RA (British Society for Rheumatology Biologics Register) cohort investigating treatment non-response and adverse events with biologics. A systematic review and network meta-analysis studied published data on treatment related adverse events with JAK inhibition.

Results

This thesis demonstrates how patient factors, particularly disability and depression, are predictive of flare events in the context of remission and drug tapering, whilst confirming that laboratory biomarkers are less helpful. In the examination of treatment non-response, polypharmacy, a surrogate measure of

comorbidity, associates with biologic therapeutic inefficacy and adverse events. Advancing age predicts treatment discontinuation. In an older cohort, combining biologic therapy with methotrexate influences the cause of treatment failure. Patients receiving a TNF inhibitor as monotherapy were less likely to discontinue treatment due to inefficacy and more likely to terminate therapy from adverse events.

Infection is one of the most important treatment related adverse events in RA. This thesis quantifies the burden of non-serious infection, affecting 1 in 8 patients who are prescribed biological therapy each year. Non-serious infection predictors parallel those observed with serious infection including increasing age, comorbidity, corticosteroid therapy, RA disease activity and disability. Biologic treatment strategies predict non-serious infection, the highest risk observed with IL-6 inhibition. Systematic review and meta-analysis of JAK inhibition trials showed the rate of serious infection is low. One non-serious infection, *Herpes zoster*, appeared as a safety signal associated with JAK inhibition. An increased incidence of herpes zoster was confirmed for all licensed JAK inhibitors, and although the risk was greatest with baricitinib, the signal is likely to be a 'class effect'.

Conclusion

To improve outcomes in RA we must draw on trial and real-world data to help us better understand clinical phenotypes and to identify those most likely to succumb to adverse events. The work presented in this thesis adds new knowledge to the efficacy and safety profiles of a complex therapeutic armamentarium. Some findings challenge existing dogma; for example, depression and disability are better predictors of treatment response than our laboratory biomarkers. Other findings will help inform national treatment guidelines.

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Publications incorporated in this thesis

Bechman K, Tweehuysen L, Garrood T, Scott DL, Cope AP, Galloway JB, Ma MHY. Flares in Rheumatoid Arthritis Patients with Low Disease Activity: Predictability and Association with Worse Clinical Outcomes. J Rheumatol. 2018 Nov;45(11):1515-1521. dx.doi.org/10.1136/rmdopen-2018-000676

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Bechman K, Halai K, Yates M, Norton S, Cope AP, Hyrich KL, Galloway JB. Non-serious infections in patients with rheumatic arthritis; results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Under review by the Lancet Rheumatology.

Personal contribution

This thesis is a compilation of work performed during my time as a clinical training research fellow in the Centre for Rheumatic Diseases at King's College London. I was awarded a prestigious Medical Research Council grant to undertake this fellowship.

The conception and development of the thesis aims were my own, with support and guidance from my supervisors, Dr James Galloway and Professor Andrew Cope.

The quantitative analyses of the REMIRA, OPTTIRA and BSRBR-RA cohorts were my own work including design, data analysis and write up. I received input from my supervisors with the methodology and interpretation of results. Dr Sam Norton provided additional statistical support.

I was invited by the editorial team of the Pharmacological Research Journal to write the review of JAK inhibition in rheumatic disease, which I undertook with input from Dr James Galloway.

I designed and performed the systematic review of safety outcomes with JAK inhibition with assistance from a second reviewer to confirm appropriate article identification. Meta-analyses and write up were my own work with statistical support from Dr Sam Norton.

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This PhD has allowed me to develop and enhance my research skills, providing a strong foundation for a future academic career, whilst cultivating a real passion in the area of immune mediated inflammatory diseases.

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Chapter 1. Background

1.1 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is the most prevalent inflammatory joint disease. Despite great advances in treatment, the condition remains incurable. In the UK it affects around 0.5-1% of the population. The disease results from a complex interaction between genes and environment, leading to a breakdown of immune tolerance. RA is a heterogeneous condition, its presentation and disease course being highly variable both within, as well as between individuals. Advances in its management have radically shaped clinical outcomes, with improvements in disease activity, functional disability, joint damage and ultimately quality of life. The remarkable heterogeneity of RA in its presentation, natural history and drug responsiveness means that it remains as challenging to manage as it is fascinating to study.

1.1.1 Aetiology

History

The first description of RA is found in the dissertation of Augustin Jacob Landré-Beauvais from the year 1800 (Landre-Beauvais, 2001). Despite classifying RA as a relative of gout, his work encouraged others to study the disease. In 1859, Alfred Garrod categorized RA as a condition distinct from gout. His son, Archibald Garrod, established the term "Rheumatoid Arthritis" in 1890. The American physician Charles Short hypothesized that RA was in fact a disease of our modern era tracing back to the 17th century, with no convincing evidence of its existence prior to this in human palaeopathology, literature or art. As such, he proposed the possibility of an environmental cause (Short, 1974).

Geographical prevalence

Although many possible aetiologies have been identified, the exact cause of RA is unknown. It is widely accepted that the disease results from a complex interaction between genetics and the environment. The predilection for RA in certain populations supports a genetic role in disease risk. The prevalence in Europe and North America is between 0.5 and 1%. A higher occurrence is described in native American-Indian populations, whilst a low prevalence is reported in Southeast Asia, with little or no reported cases in studies from rural Africa (Silman and Pearson, 2002). Migrant studies support a genetic susceptibility, with RA occurring less frequently in Black-Caribbean than Caucasians living in the same urban area in the UK (MacGregor et al., 1994).

Twin studies and heritability

Twin studies may suggest the degree to which genetic and environmental factors influence RA aetiology. Concordance rates are reported at 15% in monozygotic twins and 3.5% in dizygotic twins (SILMAN et al., 1993). However these rates are dependent on the background population prevalence. Heritability analyses using UK and Finnish twin studies provides quantitative estimates of the genetic influence on aetiology, suggestive the heritability lies between 53-65% (MacGregor et al., 2000). Other studies suggest that genetic factors contribute less than the environmental. A prospective cohort of 121,700 female nurses reported a population attributable risk of 41% for environmental factors and 21% for familial history (Sparks et al., 2014).

HLA-DRβ chain and the shared epitope

The most established genetic association in RA is the occurrence of a set of alleles encoded by the human leukocyte antigen (HLA) DRβ*1* gene locus, termed the HLA-Dw4 serotype, which is reported

more frequently among RA patients (Stastny, 1978). A portion of the HLA-DRβ chain molecule, a five amino acid sequence motif, is thought to be most closely linked to disease and has been termed the 'shared epitope'. The molecular mechanisms by which the shared epitope affects susceptibility and severity of RA are thought to be linked to the presentation of arthritogenic antigens and recognition by cognate receptors – the T cell antigen receptors. Other genetic polymorphisms have been associated with RA, including single nucleotide polymorphism of the protein tyrosine phosphatase N22 (PTPN22) gene that encodes a phosphatase involved in intracellular T cell signalling (Begovich et al., 2004), and STAT4 which encodes a transcription factor that transmits signals induced by several key cytokines (Remmers et al., 2007). Based on genome wide association studies well over 100 allelic variants have now been confirmed to be associated with seropositive RA (Viatte et al., 2013).

Smoking

Smoking is an important risk factor for RA, with a 2-fold increased risk of developing the condition in smokers. Smoking intensity and duration are both implicated, with the risk persisting even after cessation (Costenbader et al., 2006). Possible pathogenic mechanisms include oxidative stress, inflammation, autoantibody formation and epigenetic changes (Chang et al., 2014). This risk is greatest for patients who carry serum autoantibodies termed seropositive RA. A genetic environmental interaction has been described in patients with the HLA-DRB1 'shared epitope' genotype. In these patients, smoking contributes to citrullination of self-antigens. This is defined as a post-translational protein modification, involving the conversion of the amino-acid arginine into citrulline. In 60-70% of patients, this modification leads to the development of autoantibodies against citrullinated proteins termed anti-citrullinated protein antibody (ACPA) which drives RA pathogenesis (Padyukov et al., 2004, Klareskog et al., 2006). Interestingly, ACPA can be detected up to 14 years before disease onset,

suggesting that this immune reaction is a very early event in the natural history of the disease (Nielen et al., 2004, Rantapaa-Dahlqvist et al., 2003).

Infection

Microbial infections are also believed to contribute to the aetiopathogenesis of RA. Common associated microbes include *Porphyromonas gingivalis* (*P. gingivalis*), *Proteus mirabilis* (*P. mirabilis*), Epstein–Barr virus (EBV) and mycoplasma (Li et al., 2013). An association with periodontitis, tooth loss and RA has been demonstrated in multiple clinical studies (de Pablo et al., 2008, Dissick et al., 2010, de Smit et al., 2012), with significantly higher concentrations of antibodies to *P. gingivalis* among RA patients than seen in controls (Mikuls et al., 2009) and periodontal bacterial DNA detected in serum and synovial fluid of RA patients with refractory disease (Martinez-Martinez et al., 2009). *P. gingivalis* contains the enzyme peptidyl arginine deiminase (PADI), which allows the bacteria to generate citrullinated peptides. *P. gingivalis* antibody concentrations have been shown to correlate with expression of ACPA. Several studies have revealed that the composition of the intestinal microbiota is altered in patients with RA. An increase abundance of certain bacteria e.g. *Prevotella copri* have been observed in early RA, with a reduction in others including Bacteroides species. These organisms are thought to influence the innate and adaptive immune response (Maeda and Takeda, 2017).

Hormonal factors

There is an increased prevalence of RA among women suggesting that hormonal factors play a role in the disease aetiology, although the exact role is not yet understood. Controversies exist regarding which hormonal factors are protective and which increase risk. Low levels of oestrogen as seen with an earlier age at menopause, exogenous oestrogen from sources such as HRT or periods of hormonal

change have all been described (Alpízar-Rodríguez et al., 2016). Pregnancy is thought to be protective in both RA development and in RA disease activity. Disease activity often ameliorates during pregnancy with relief noted from the first trimester and returns again in the post-partum period. Disease activity modulation has been explained by multiple hormonal, neuroendocrine and immunological factors (Nelson and Østensen, 1997).

1.1.2 Pathophysiology

Early innate and adaptive immune responses

The exact cause of RA is unknown. In a genetically predisposed individual, an infective agent or another stimulus binds to toll-like receptors on peripheral dendritic cells and macrophages. This triggers a rapid response of the innate immune system, stimulating the release of cytokines, complement and inflammatory mediators, whilst activating natural killer cells and neutrophils (Scott and Kingsley, 2006). Dendritic cells migrate to lymph nodes and assume the role of antigen-presenting cells, displaying antigen bound on major-histocompatibility-complexes to the T cell receptor. This activates T cells, initiating the adaptive immune response, leading to cell proliferation and migration to the joint synovial membrane. Some T cell are activated within the synovium by interaction with other antigen-presenting cells including macrophages and B cells (Smolen and Steiner, 2003) (Figure 1).

Cytokine production and inflammatory mediators

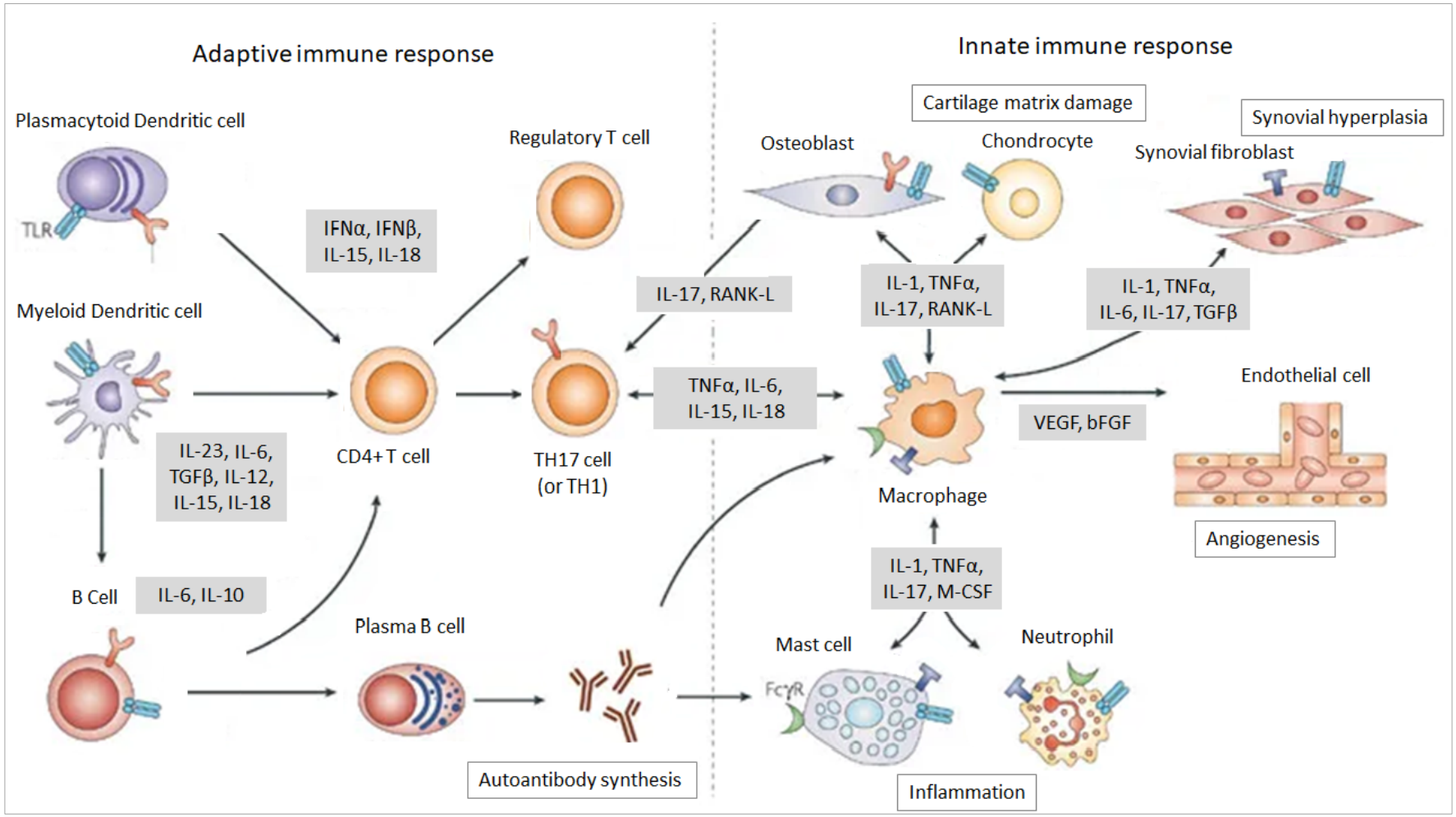
Activated T cells produce interleukin-2 (IL-2), interferon-γ (IFN-γ), tumour necrosis factor alpha (TNFα) and granulocyte-macrophage-colony stimulating factor (GM-CSF) which stimulate monocytes, macrophages, fibroblasts, chondrocytes and osteoclasts (McInnes and Schett, 2011). Activated

macrophages and fibroblasts within the synovium release further proinflammatory cytokines including TNF-α, IL-1 and IL-6. These cytokines stimulate the production of additional inflammatory mediators including chemokines, tissue-degrading enzymes (matrix metalloproteinases MMPs), co-stimulatory and adhesion molecules (O'Shea et al., 2015, Smolen and Steiner, 2003) and growth factors (fibroblast growth factor-2 and vascular endothelial growth factor) amplifying the inflammatory process.

Table 1. Examples of key cytokines in the pathology of rheumatoid arthritis (Choy, 2012, McInnes and Schett, 2007)

Cytokine	Potential functions in the pathogenesis of RA
TNF-α	Activates leucocytes, endothelial cells, synovial fibroblasts stimulating the production of cytokines, chemokines, adhesion molecules and matrix enzymes Activates osteoclast and resorption of cartilage and bone Supresses regulatory T cell function Induces expression of vascular endothelial growth factor (VEGF) promoting angiogenesis Implicated in hypothalamic pituitary adrenal axis dysfunction (fatigue and depression) Implicated in cardiovascular disease promotion
IL-6	Drives neutrophil recruitment Involved in B cell differentiation, proliferation and antibody production Stimulates proliferation and differentiation of T cells Actives osteoclast and resorption of cartilage and bone Induces expression of vascular endothelial growth factor (VEGF) promoting angiogenesis Stimulates hepatic acute-phase response Promotes anaemia via hepcidin production Implicated in hypothalamic pituitary adrenal axis dysfunction (fatigue and depression)

Figure 1. The innate and adaptive compartments of the inflammatory response (McInnes and Schett, 2007)



This figure illustrates the innate and adaptive compartments of the inflammatory response in RA. The activation of dendritic cells, T cells, B cells and macrophages and the dysregulated expression of cytokines drive activation of neutrophils, mast cells, endothelial cells and synovial fibroblasts.

Important role of immune cells

The immunogenetics of RA suggests a key role of the T cell in disease initiation. Proinflammatory T-helper (Th)1 effector cells promote many aspects of synovial inflammation. T cell subsets with regulatory capacity (T-regs) are functionally impaired allowing Th1 driven immunity to evolve and progress into chronic inflammation (Leipe et al., 2005). Type 17 helper T cells (Th17) also have a role. These cells produce IL-17 which activates fibroblasts and chondrocytes (McInnes and Schett, 2011) although the therapeutic impact of IL-17 inhibition in RA is modest compared to that seen in psoriatic arthritis.

B cells contribute to pathogenesis through antigen presentation and by the production of antibodies and cytokines. Autoantibodies form larger immune complexes that further stimulate the production of pro-inflammatory cytokines, through complement and Fc-receptor activation.

In addition to their role in antigen presentation, macrophages drive many of the pro-inflammatory pathways within the synovial tissue and are a major source of cytokine production (McInnes and Schett, 2007). They are also involved in osteoclastogenesis (Choy, 2012). TNF-α and IL-1 induce receptor activator of NF-κB (RANK) expression on macrophages, which interact with RANK ligand on T cells, neutrophil and fibroblasts. This drives macrophage differentiation into osteoclasts that resorb and destroy bone (Drexler et al., 2008).

Synovial fibroblasts maintain chronic inflammation secreting cytokines and chemokines and are responsible for excessive matrix degradation that destroys cartilage. A functionally distinct fibroblast subset has been identified in RA patients, with a pathogenic role in matrix invasion, immune cell recruitment and osteoclastogenesis (Mizoguchi et al., 2018).

Inflammatory cell signalling

Perturbation of cell signal transduction pathways are implicated in the pathogenesis of RA. These pathways facilitate the immune response. Ligands bind to cell surface receptors activating an intracellular signal transduction cascade. This results in the genetic transcription of important mediators involved in cell proliferation and differentiation, and the expression of pro-inflammatory cytokines and other effector molecules. Multiple cytokines signal through the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. (This will be discussed in more details in section 1.17 JAK-STAT pathway). Another important pathway involves the stress- and mitogen-activated protein kinases (SAPK/MAPK), which include extracellular signal–regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. All three signal transduction pathways are activated in the course of synovitis, with phosphorylated forms of the ERK, JNK and p38 MAPK overexpressed in rheumatoid synovial tissue (Schett et al., 2000). p38 MAPK is considered to be one of the most important signals for TNF-mediated inflammatory responses (Schett et al., 2008).

1.1.3 Epidemiology

In the UK, there are approximately 422,000 patients aged 16 years or older diagnosed with RA, with around 350,000 in England alone (NICE, 2018b). Women are affected 2-3 times more often than men. The annual incidence for males and females is 2.5 and 5.4 per 10,000 respectively. This equates to approximately 17,500 diagnoses each year in England and 21,000 across the UK. The peak age of onset is between 50 and 75, although RA can present at age. The condition affects all populations, though its prevalence varies by ethnicity (1% in Caucasians, 0.1% rural Africans, 5% in Chippewa Indians) (Spector, 1990).

1.1.4 Clinical features

Joint involvement

RA is defined by the involvement of synovial-lined joints. Although it can affect any joint, the metacarpophalangeal, proximal interphalangeal, metatarsophalangeal, wrists and knees are the most commonly involved. Presentation is often insidious in onset, characterised by symmetrical polyarticular involvement with pain, stiffness and swelling. Twenty five percent of patients have an acute or subacute presentation. Less frequently joint involvement may present as palindromic (recurrent, resolving episodes of oligoarthritis), monoarticular, peri-articular with tenosynovitis or bursitis, or polymyalgia-like (clinically indistinguishable from polymyalgia rheumatica). The symptoms of synovitis show diurnal variation with exacerbations in the morning. This is thought to relate to circadian alterations in immune and inflammatory responses (Harkness et al., 1982).

Extra-articular manifestations

Involvement outside of the joint, including bone, muscle and other organs occurs in 40% of patients with RA (Myasoedova et al., 2011), and is associated with severe disease and increased morbidity and mortality (Turesson et al., 2002). Constitutional symptoms including fatigue, malaise, fever and weight loss can predate the onset of articular symptoms by several months. Fatigue is seen in 40-80% of patients (Wolfe et al., 1996, Pollard et al., 2006). It is strongly associated with pain and depression, and likely mediated centrally (Pollard et al., 2006). It is also influenced by psychosocial factors and health beliefs (Wolfe and Michaud, 2004).

Bone loss in RA may be systemic, periarticular or focal (Deal, 2012). Systemic osteoporosis is driven by inflammation, immobility and iatrogenic steroid therapy. Patients with RA have a 30% increased risk of

a major osteoporotic fracture and a 40% increased risk of hip fracture (Kanis et al., 2008). Muscle weakness in RA is multifactorial. Synovitis leads to decrease joint motion and resulting muscle atrophy, which may be exacerbated by drug induced myopathy. Myositis in RA is rare (Ancuta et al., 2014).

RA can also manifest with cutaneous, ocular, pulmonary, cardiac, renal, neurological and haematologic manifestations. Keratoconjunctivitis sicca and xerostomia, the characteristic features of Sjogren's syndrome are the most common ophthalmic manifestation. Episcleritis and scleritis occur in less than 5% of patients, whilst necrotizing scleritis and corneal melting has significantly reduced over the last 20 years (Zlatanović et al., 2010). Interstitial lung disease is the most frequent pulmonary manifestation, occurring within the first decade of onset of RA with a predominant usual interstitial pneumonia (UIP) pattern in two-thirds of patients (Kelly et al., 2014).

1.1.5 Diagnosis and classification criteria

History and examination

The diagnosis of RA requires a careful history and examination which is often supported by laboratory investigations. History should focus on the location of joint involvement and the degree of joint symptoms including pain, swelling and at least 30 minutes of morning stiffness. The duration of symptoms should be determined. A duration of less than 6 weeks may be viral in aetiology. Important differential diagnoses including other inflammatory arthritides (psoriatic, enteropathic and reactive), connective tissue disease or vasculitis. Clinical examination allows the identification of synovitis, with an assessment of the number of tender and swollen joints and an evaluation of extra-articular manifestations.

Laboratory tests including autoantibodies

Laboratory tests supporting the diagnosis of RA include raised markers of systemic inflammation; the erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP), and positive antibodies tests with rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). RF antibodies are directed against the Fc portion of immunoglobulin G (IgG), and were the first autoantibodies found to associate with RA. Although their exact role is not defined, they form immune complexes and induce complement activation which promote the production of inflammatory mediators. RF has diagnostic and prognostic implications. It is seen in 70-90% of patients with RA, although it is also found in healthy individuals and in other autoimmune and infectious diseases (Dorner et al., 2004). It associates with a more severe disease course and erosive radiographic progression (Carpenter et al., 2016, Aletaha et al., 2013).

ACPA constitute a growing family of autoantibodies. Antiperinuclear factor (APF) was the first ACPA described, over 40 years ago. ACPA are directed against citrulline containing epitopes, which are generated via post-translational modification of arginine. Citrullination is a normal physiological process that occurs during apoptosis and inflammation. However less than 1% of the population develops ACPA. Current literature suggests that the initiation of an HLA class II restricted T-cell response to citrullinated proteins only occurs in genetically predisposed individuals (e.g., shared epitope) (Raptopoulou et al., 2007). Recognition of citrullinated proteins by ACPA leads to immune complex formation, complement activation and the direct stimulation of macrophages leading to TNF-α secretion. They also enhance the formation of neutrophil extracellular traps (NETs) leading to further generation of citrullinated antigens perpetuating the inflammatory response (Yu and Lu, 2019). Compared to RF, ACPA demonstrate a similar sensitivity but a higher specificity, distinguishing RA from other rheumatic disease (Avouac et al., 2006). They are also superior in predicting erosive disease (Nishimura et al., 2007). Both RF and

ACPA can present before the onset of disease, defining a 'pre-clinical phase of RA'. This can be useful in identifying patients with undifferentiated arthritis who will progress to RA (van Gaalen et al., 2004).

Seronegative RA is defined by a negative RF and ACPA blood test. It is more challenging to classify and may represent a heterogeneous population or possibly a distinct genetic disease with its own pathogenesis. Less is known about the clinical presentation and outcomes of seronegative RA (Ajeganova and Huizinga, 2015). Although generally a more favourable prognosis is expected, seronegative RA does not greatly differ from overall RA in terms of management options, therapeutic response and structural and functional damage (Lukas et al., 2019).

Imaging

Conventional radiography has been the imaging modality of choice for detecting structural damage. Several scoring systems have been developed to quantify articular damage, including the Sharp/van der Heijde (van der Heijde, 2000) and Larson scores (Larsen, 1995, Scott et al., 1995). These are however insensitive to early bone involvement and do not directly demonstrate inflammation. Ultrasonography and magnetic resonance imaging (MRI) are increasingly employed in clinical practice and research, with sensitivity in detecting inflammation (synovitis, tenosynovitis, bursitis and for MRI bone marrow oedema) and identifying evidence of early bone erosion.

Classification criteria

In rheumatic diseases, classification criteria allow a universal definition of a disease that can be used to compare across studies and centres and enable the standardised recruitment of patients into clinical trials. The 1987 American College of Rheumatology (ACR) criteria were formulated to distinguish

patients with established RA from other rheumatic diseases (Arnett et al., 1988). These were replaced by the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria for RA, established to identify patients presenting with early inflammatory synovitis who are at risk of persistent and/or erosive disease, and thus should be considered for intervention with conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) (Aletaha et al., 2010). These classification criteria should only be applied when there is evidence of active clinical synovitis (defined as joint swelling) in at least 1 joint and the observed synovitis is not better explained by another diagnosis. Patients achieving a score of $\geq$ 6 derived from four domains are considered to fulfil the classification criteria (Figure 2).

NICE RA quality standards

It is now widely accepted that early therapeutic intervention improves clinical outcomes and reduces radiographic damage and disability in RA (van der Heide et al., 1996). It is therefore paramount that a diagnosis is made in a timely fashion. The National Institute for Health and Care Excellence (NICE) published quality standards advising that patients who present to general practice with suspected persistent synovitis of the small joints of the hands or feet, or more than one joint, are referred to a rheumatology service within 3 working days of presentation. Patients should then be assessed within 3 weeks of referral, and if a diagnosis of RA is made, they should be offered csDMARD monotherapy within 3 months of onset of their symptoms (NICE, 2018b). The rationale behind these quality standards is to avoid delays in diagnosis and increase the likelihood of early treatment initiation. Early treatment is associated with better long-term outcomes.

Figure 2. The 2010 ACR/EULAR classification criteria for rheumatoid arthritis (Aletaha et al., 2010)

Target population:	
1) Have at least 1 joint with definite clinical synovitis	
2) Synovitis is not better explained by another disease	
A. Joint involvement	*Score*
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
6 weeks	0
6 weeks	1

1.1.6 Prognosis

At the end of the last century, the prognosis for RA was poor. The condition was associated with significant morbidity and increased mortality. Advances in therapeutics and earlier drug intervention had resulted in vast improvements in clinical outcomes. None-the-less, RA remains an incurable disease. Patients are still at risk of long-term complications including functional decline, reduced quality of life and work disability. At disease onset, 28% of patients are unable to work. After 15 years, this increases to 45% (Eberhardt et al., 2007).

A meta-analysis of studies published over the last 50 years suggests a standardized mortality ratio of 1.47, suggesting patients with RA have a 47% increased risk of death compared to the general population (Dadoun et al., 2013). Causes of morbidity and premature mortality include cardiovascular disease, infections and lymphoproliferative malignancy. More recent studies confirm that mortality rates have remained elevated and have not changed significantly over the last 20 years (Humphreys et al., 2014).

1.1.7 Management

Conventional Synthetic Disease Modifying Antirheumatic Drugs (csDMARDs)

The management of RA is unrecognisable from that 30 years ago when there were fewer available agents, some of which had limited efficacy. In the early 20th century treatment was aimed at symptomatic benefit, including splinting, physical therapy, bed rest, analgesia and salicylates. Gold salts were first used in the 1920s, later demonstrating therapeutic efficacy in small clinical trials. This was followed by the discovery of glucocorticoids and its biological effects, earning Philip Hench, Edward Kendall and Tadeus Reichstein the Nobel Prize in Medicine. The first patient treated by Hench with Compound E (cortisone) had RA. The effect of steroid was 'miraculous' (Hench et al., 1949). Treatment options subsequently expanded to include other medications such as parenteral gold salts, sulfasalazine, chloroquine, hydroxychloroquine, D-penicillamine, ciclosporin and azathioprine. These drugs were termed conventional synthetic disease modifying antirheumatic therapies (csDMARDs) (Upchurch and Kay, 2012).

Although methotrexate has been used in the treatment of childhood leukaemia since the 1950s, it was several decades later before it gained FDA approval in RA. Despite positive results from open studies, the first placebo-controlled trials were not performed until the mid-1980s (Weinblatt, 2013). By the 1990s methotrexate was the initial drug of choice. The initial pyramid approach of first-line non-steroidal anti-inflammatory drugs (NSAIDs) followed later by the introduction of csDMARDs was inverted. A new treatment paradigm emphasized early and consistent use of csDMARDs. Studies reported benefit from combination therapy with multiple csDMARDs and corticosteroids, an approach that continues today (O'Dell et al., 1996, Landewe et al., 2002).

Mechanism of action of csDMARDs

The precise mechanism of action of methotrexate is unknown. It demonstrates antiproliferative properties. As a structural analogue of folic acid, methotrexate competitively inhibits the conversion of dihydrofolic acid to its active metabolite folinic acid, interfering with purine and pyrimidine metabolism. However its effects on adenosine signalling is the most widely accepted explanation for its mechanism of action. Methotrexate increases extracellular adenosine levels, which act at adenosine receptors on inflammatory cells triggering an intracellular cascade and promoting an anti-inflammatory state (Cronstein, 2005). Other proposed mechanisms of action include apoptosis of peripheral T cells (Genestier et al., 1998), suppression of T cell activation and adhesion molecule expression (Johnston et al., 2005) and a decreased production of proinflammatory cytokines (Gerards et al., 2003).

Like methotrexate, the precise mechanism of action of sulfasalazine has not been fully elucidated. Its anti-inflammatory effects include suppression of B- and T-lymphocyte proliferation, inhibition of IL-1, IL-2, IL-6, IL-12 and TNFα release, IgM and IgG production (Rodenburg et al., 2000) and promotion of extracellular adenosine (Gadangi et al., 1996). It also modulates receptor activation of NFkB, osteoprotegerin (OPG) and RANK-ligand, inhibiting osteoclastogenesis (Lee et al., 2004). Leflunomide exerts its effects by inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase which is required for pyrimidine synthesis. This is essential for the proliferation of T lymphocytes, which require sufficient pyrimidines to support DNA synthesis (Breedveld and Dayer, 2000). Hydroxychloroquine is an antimalarial. It exerts its effects on the innate immune system, blocking the stimulation of toll-like receptors (Lafyatis et al., 2006). It is lysosomotropic, raising the intracellular pH, perturbing cycling of intracellular proteins and interfering with post translational modification of protein and antigen processing by macrophages and other cells (Fox, 1993).

Guidelines on csDMARD treatment

NICE guidelines recommended first-line treatment with either oral methotrexate, leflunomide or sulfasalazine monotherapy, ideally within 3 months of symptoms onset, with the dose being escalated as tolerated. Hydroxychloroquine is considered an alternative for mild or palindromic disease. Glucocorticoids can be offered as a short-term bridging treatment when starting csDMARDs. Combination therapy in a step-up strategy should be considered when the treatment target of remission or low disease activity has not been achieved (NICE, 2018a). EULAR guidelines (updated in 2016) recommend methotrexate as part of the first treatment strategy, either as monotherapy or in combination with other csDMARDs (Smolen et al., 2017b). All guidelines recommend starting therapy as soon as the diagnosis of RA is made and adopting a treat-to-target strategy, aiming for low disease activity or sustained remission.

Biological Disease Modifying Antirheumatic Drugs (bDMARDs)

The introduction of biologic agents (biological DMARDs, bDMARDs) has revolutionized the management of RA. Their development was the culmination of decades of research, identifying key mediators and cell subsets that drive the inflammatory process in RA.

TNF inhibitors (TNFi)

TNF inhibitors were one of the first genetically engineered protein in RA, designed to target the cytokine tumour necrosis factor alpha (TNFα). The theory arose that increased concentrations of TNFα at sites of inflammation were fuelling disease (Brennan et al., 1989). Transgenic mice overexpressing human TNFα developed arthritis which was clinically and histopathologically similar to RA (Keffer et al., 1991). A crucial first proof of principle clinical trial was performed in 1993 with the drug cA2, a chimeric (mouse

and human) monoclonal antibody (mAbs) in 20 patients with active RA. Treatment with cA2, now licensed as infliximab, was associated with significant clinical and laboratory improvements (Elliott et al., 1993). This opened the era of multiple RCTs demonstrating unequivocally the efficacy of biologics targeting TNFα.

To date, five drugs that inhibit TNFα are licensed for use in RA. All TNF inhibitors (TNFi) except etanercept are mAbs or fragments thereof (Figure 3). Each drug within the TNFi class differs in its molecular structure and pharmacokinetic property. Agents demonstrate varying degrees of avidity for soluble and membrane bound TNFα, and differing dissociation capacity with some forming more stable complexes with TNF-α than others (Mpofu et al., 2004).

Efficacy of first generation TNFi

All three TNFi have demonstrated significant efficacy in placebo-controlled trials in both early and established RA. In established RA, the pivotal phase III ATTRACT trial compared infliximab with placebo, in combination with methotrexate, demonstrating significant improvements in disease activity and prevention of erosive progression (Maini et al., 1999). Several studies have replicated and extended these data (Lipsky et al., 2000, Kavanaugh et al., 2000). In early disease, the ASPIRE (St Clair et al., 2004) study investigated infliximab with methotrexate demonstrating superior efficacy over methotrexate alone. The BeSt (Goekoop-Ruiterman et al., 2005) study compared four treatment strategies, one of which involved early introduction of combination methotrexate and infliximab, confirming that infliximab induced a remission state that was maintained upon cessation of infliximab therapy.

Adalimumab has been assessed in 5 major placebo controlled RCTs. In established disease, the ARMADA study demonstrated adalimumab in conjunction with methotrexate was superior to placebo in reducing erosive progression and improving clinical responses (Weinblatt et al., 2003). These findings were maintained at 4 years of follow up (Weinblatt et al., 2006). The DE019 trial (Keystone et al., 2004) reported similar results, whilst the DE011 trial demonstrated efficacy of adalimumab as monotherapy (van de Putte et al., 2004). In early RA, the PREMIER study found adalimumab and methotrexate combination was significantly superior to either methotrexate or adalimumab monotherapy (Breedveld et al., 2006).

Etanercept has been evaluated in 5 major RCTs, 3 studying its efficacy as a monotherapy and 2 in combination with methotrexate. In established RA, the earliest phase III trial reported rapid and sustained improvement when etanercept was added to methotrexate therapy (Weinblatt et al., 1999). The TEMPO study demonstrated superior efficacy with combination etanercept methotrexate compared with either drug alone (Klareskog et al., 2004). The ADORE study confirmed that the addition or substitution with etanercept resulted in substantial improvement, with no difference in etanercept monotherapy compared to combination therapy (van Riel et al., 2006). In early RA, etanercept monotherapy demonstrated rapid rates of improvement and superiority in reducing disease activity and arresting structural damage (Bathon et al., 2000). The COMET study assessed etanercept methotrexate combination as first line therapy in methotrexate naive patients with 50% of patients achieving clinical remission at 1 year (Emery et al., 2008a).

Efficacy of second generation TNFi

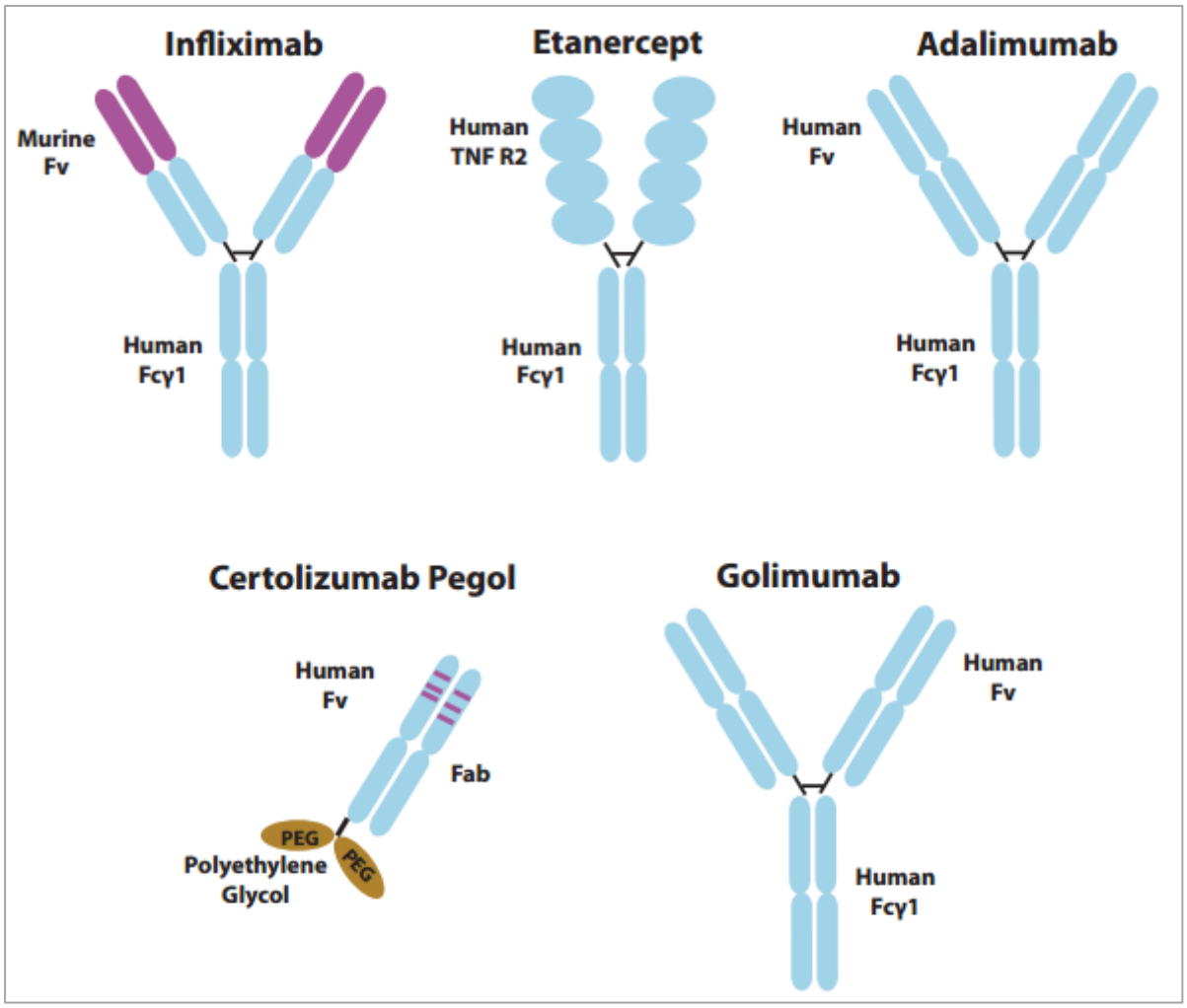
The frequency of primary and secondary non-response, defined as either i) no initial response or ii) a loss of response over time, has contributed to the development of second-generation TNFi

certolizumab pegol and golimumab. In the RAPID trials, certolizumab was superior to placebo in methotrexate non-responders (Keystone et al., 2008, Smolen et al., 2009a). The REALISTIC trial stratified patients according to prior TNFi use and concomitant methotrexate. The study demonstrated rapid clinical responses with certolizumab versus placebo irrespective of previous or concomitant therapy (Weinblatt et al., 2012). Induction of remission was evaluated in the CERTAIN trial, with a loading regimen shown to improve the speed of therapeutic action (Smolen et al., 2015), whilst the FAST4WARD trial assessed certolizumab effectiveness as monotherapy (Fleischmann et al., 2009). The efficacy of golimumab was demonstrated in methotrexate-naïve patients with early RA (GO-BEFORE) (Emery et al., 2009), methotrexate inadequate responders (GO-FORWARD) (Keystone et al., 2009), and in those who had failed a prior TNFi agent (GO-AFTER) (Smolen et al., 2009b).

Efficacy between TNF inhibitors

Differences in study design between the TNFi trials may account for differences in efficacy. Unfortunately, there are few head-to-head studies comparing the efficacy of one agent to another. In the absence of superiority studies, indirect comparisons provide the best evidence for demonstrating differences between agents. The Cochrane review demonstrated no difference in response between the first-generation TNFi (Singh et al., 2009). Other meta-analyses have demonstrated similar results (Kristensen et al., 2007). Analyses comparing newer TNFi agents certolizumab and golimumab have not revealed improved efficacy over already existing first-generation TNFi (Aaltonen et al., 2012). Overall, indirect treatment comparisons have found no significance difference in efficacy between all TNFi therapies (Devine et al., 2011).

Figure 3. The structure of TNF inhibitors(Bechman K, 2016).



This figure illustrates the structure of TNFi. Infliximab is a chimeric mAb, 25% murine and 75% human, derived with a constant human region IgG1 and a variable mouse region. Adalimumab is a fully human-sequence IgG1 antibody. Etanercept is a recombinant human TNF-receptor fusion protein. Certolizumab pegol contains a TNF-specific Fab fragment of a humanised mAb and a fragment conjugated to 40-kDa polyethylene glycol to enhance its plasma half-life. It does not contain an Fc region and therefore does not bind complement or cause antibody-dependent cell-mediated cytotoxity. It is also less likely to cross the placenta with implications for use in pregnancy. Golimumab is a fully human IgG mAb. All agents have affinity for both soluble and transmembrane forms of TNFα, neutralising its function by blocking interaction with cell-surface TNF receptors.

IL-6 inhibition

Early animal studies have demonstrated the pivotal role of IL-6 in the pathogenesis of RA. The first agent developed to target the IL-6 pathways was tocilizumab, which has been licensed for almost a decade. Like tocilizumab, sarilumab is a humanised mAb that binds the IL-6 receptor and has only recently been approved in both the US and the EU.

Efficacy of interleukin-6-receptor inhibitors

Three placebo-controlled trials assessed tocilizumab in patients who had failed to respond to methotrexate (OPTION and LITHE)) (Smolen et al., 2008, Fleischmann et al., 2013) or csDMARDs (TOWARD) (Genovese et al., 2008), with greater clinical response, reduced structural joint damage and improved physical function. Efficacy after TNFi failure was assessed in the RADIATE trial with greater clinical response and significantly more patients with disease remission compare to placebo (Emery et al., 2008b). Tocilizumab monotherapy was superior to methotrexate monotherapy in methotrexate naive patients in the AMBITION study (Jones et al., 2010), whilst the ACT-RAY study suggested numerical superiority in remission rates with combination therapy compared to tocilizumab monotherapy, although not statistically significant (Dougados et al., 2013a). The ADACTA study was the first head-to-head superiority trial comparing tocilizumab monotherapy and adalimumab monotherapy, demonstrating tocilizumab superiority in all main efficacy endpoints (Gabay et al., 2013).

Sarilumab has demonstrated efficacy in combination with methotrexate in patients who have failed methotrexate (Genovese et al., 2015) and in those with an inadequate response to TNFi (Fleischmann et al., 2017c). Like tocilizumab, in the MONARCH trial sarilumab monotherapy demonstrated superiority over adalimumab monotherapy (Burmester et al., 2017b)

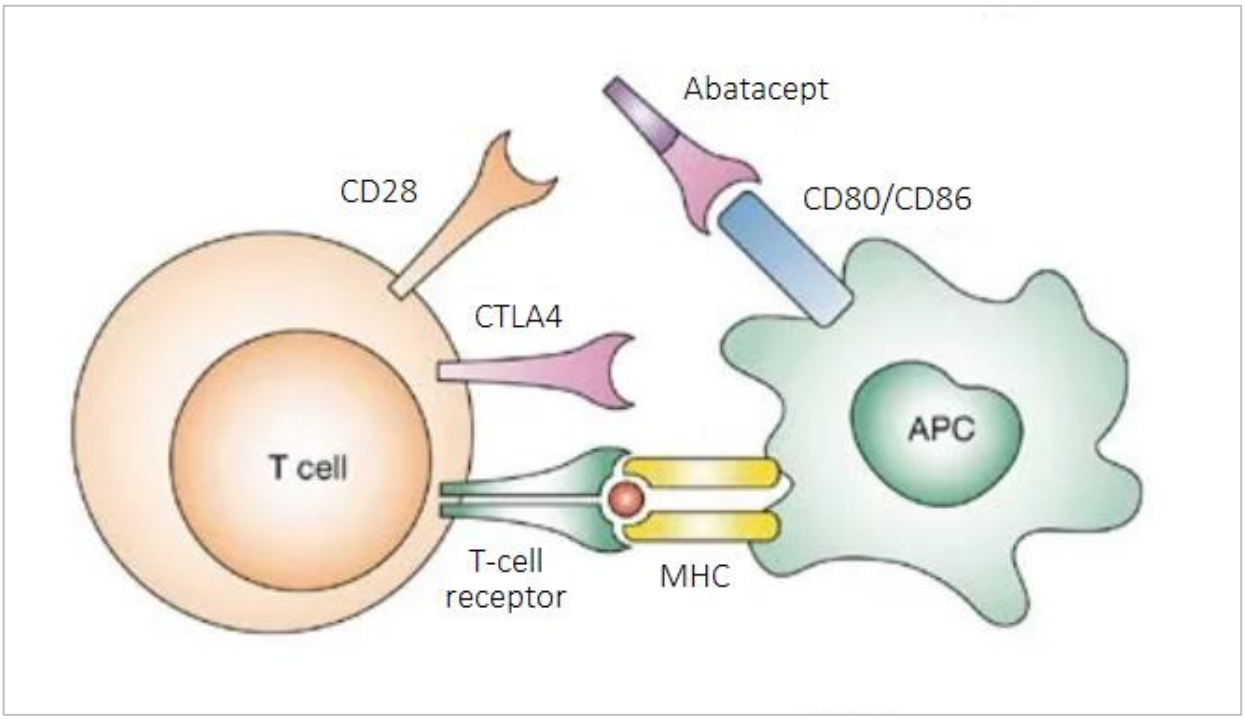
Co-stimulatory Signal Inhibition

Abatacept inhibits the co-stimulation of T cells by binding to cluster of differentiation (CD) 80/86 epitopes on antigen presenting cells and modulating its interaction with CD28 on the T cell receptor (Figure 4). This leads to reduced T cell proliferation and a decrease in the production of inflammatory cytokines. In mouse models, if administered at time of immunisation it can prevent the development of collagen induced arthritis and if given after disease onset associates with symptom improvement (Webb et al., 1996). Abatacept is a fully humanized protein construct, consisting of the extracellular domain of human cytotoxic T lymphocyte associated antigen 4 (CTL4) and a genetically engineered fragment of the Fc region of human IgG1.

Efficacy of abatacept

Abatacept has demonstrated significant improvements in disease activity, physical function and radiographic progression in placebo-controlled trials with methotrexate in early RA (Westhovens et al., 2009) and in established disease (Kremer et al., 2006). In patients with undifferentiated inflammatory arthritis, abatacept delayed the progression of inflammatory joint disease (Emery et al., 2010b). Monotherapy was as effective as methotrexate but less than combination abatacept and methotrexate (Emery et al., 2015). Efficacy over placebo was also demonstrated in patients who had failed TNFi (Genovese et al., 2005). Studies evaluating abatacept against TNFi demonstrated similar efficacy; the ATTEST trial against infliximab (Schiff et al., 2008) and a head-to-head study against adalimumab monotherapy (Weinblatt et al., 2013).

Figure 4. Mechanism of action of abatacept in the blockade of T-cell co-stimulation (Ruderman and Pope, 2006)



This figure demonstrates the mechanism of action of abatacept. T-cell activation requires both interaction between the T-cell receptor and antigen (red circle) bound to MHC molecules on an antigen presenting cell (APC), plus a second co-stimulatory signal. The most important of these is the interaction between CD28 on the T cell and CD80/CD86 on the APC. Following T cell activation, CTLA4 expression is upregulated. The interaction between CTLA4 on the T cell and CD80/CD86 on the APC suppresses further T-cell activation. Abatacept, a humanized protein construct consisting of CTLA4 and a fragment of the Fc region of human IgG1, blocks the interaction between CD80/CD86 disrupting the interaction with CD28.

B-Cell Depletion therapy – Anti-CD20

Rituximab is a chimeric molecule consisting of human IgG1 and murine variable region with CD20. CD20 is a phosphoprotein that is highly expressed by naive, mature and memory B cells, but not by early B cell precursors and antibody-producing plasma cells. Therefore, B cells may be depleted by rituximab without preventing their regeneration, whilst potentially eliminating the autoantibody-producing clones. B cell depletion is driven by antibody dependent cell mediated cytotoxicity, complement mediate cytotoxicity and the promotion of CD20+ B cell apoptosis (Shaw et al., 2003). $CD20^{+}$ B cell depletion in RA is complete 1 month after treatment and sustained for several months (Leandro et al., 2006).

Efficacy of rituximab

In the late 1990s, a case report documented remission of coexisting RA in patients treated with rituximab for non-Hodgkin lymphoma (Protheroe et al., 1999). A small open label study in 22 RA patients was the first to show the efficacy of rituximab, albeit with concomitant steroid and cyclophosphamide (Leandro et al., 2002). This was followed by a larger open label study evaluating rituximab methotrexate combination (Edwards et al., 2004). Placebo control trials continued to demonstrate efficacy in methotrexate (DANCER and SERENE) (Emery et al., 2010a, Emery et al., 2006) and TNFi non-responders (REFLEX study) (Cohen et al., 2006). Efficacy was longstanding, lasting up to a year after the initial treatment course. Combination with methotrexate was more effective than monotherapy (Owczarczyk et al., 2008).

Efficacy between biologics

There are few head-to-head superiority studies evaluating the biologic classes against each other and as such, systematic reviews have attempted to compare agents. A meta-analysis in methotrexate inadequate responders found similar clinical response in TNFi and non TNFi bDMARDs (after exclusion of the certolizumab trials). Comparing agents individually saw greater efficacy with TNFi than abatacept but not with rituximab and tocilizumab (Salliot et al., 2011). Other meta-analyses have confirmed similar efficacy between the bDMARDs (Guyot et al., 2011). Some superiority is reported with tocilizumab which may relate to the drugs influence on reducing CRP levels which are sometimes used in calculating disease response (Bergman et al., 2010). After an inadequate response to TNFi no differences were reported between agents (Salliot et al., 2011).

Biosimilars

A biosimilar is defined as a "biological medicinal products that contain a version of the active substance of an already authorized original or reference biological medicinal product' (Agency, 2011). Changes in post-translational modification and/or manufacturing processes result in a product that is highly similar but not identical to approved reference agent. Before a biosimilar is made available on the market, evidence on preclinical, pharmacokinetic, pharmacodynamic and clinical data are required to demonstrate comparable efficacy and safety (Dörner et al., 2016). Minor modification may alter function and immunogenicity which has raised concerns about switching patients who are well established on a reference biologic to a biosimilar. The infliximab biosimilars Inflectra/Remsima and Flixabi and the etanercept biosimilar Benepali were the first TNFi biosimilars to reach the European market. Since then, further biosimilars for etanercept, adalimumab and rituximab have been introduced. It has been estimated that Germany, France and the UK each stand to save between €2.3 billion and €11.7 billion between 2007 and 2020 in response to the introduction of biosimilars (Robert

Haustein, 2012). National guidelines express a preference for lower cost therapies when there is similar efficacy and safety, although recommendations do not distinguish between approved agents. Switching to a biosimilar can result in a nocebo responses, with a subjective increase in disease activity and pain-related adverse events (Smolen et al., 2019a).

National and international guidelines

British guidelines from the British Society of Rheumatology (BSR) (Luqmani et al., 2006) and NICE (NICE, 2018a) recommend TNFi therapy in patients with high disease activity who have failed a trial of two csDMARDs, including methotrexate unless contraindicated, over a 6 month period. The European (EULAR) (Smolen et al., 2017b) and American (ACR) (Singh et al., 2016a) guidelines recommend TNFi initiation in patients who have failed csDMARD monotherapy. In the European guidelines, this is stipulated for patients with poor prognostic factors. Abatacept, tocilizumab and sarilumab and rituximab can also be used as first line agents in csDMARD failure (NICE, 2018a, Smolen et al., 2017b, Singh et al., 2016a), although according to NICE recommendations rituximab should be been used after failure to one TNFi agent. Adalimumab, etanercept, certolizumab or tocilizumab can be used as monotherapy in patients who cannot tolerate methotrexate, although combination therapy with csDMARDs is preferred (NICE, 2018a). Abatacept should be preferentially used in combination with methotrexate or other csDMARDs. Therapy should be continued only if there is an adequate response at 6 months.

Switching between TNF inhibitors can be effective as intolerances may be idiosyncratic rather than a class effect. Differences between the agents in binding affinity, mechanism of action and immunogenicity may explain the success behind TNFi cycling. For example, following primary failure with a mAb, switching to the fusion protein etanercept can prove efficacious possibly due to

etanercept's ability to the bind proinflammatory lymphotoxin-α in addition to TNFα (Buch et al., 2004). Equally, the presence of neutralizing antibodies to a mAb may result in waning efficacy and switching to a mAb with a different molecular structure or epitope target may prove beneficial. The response to subsequent TNFi agents is influenced by the reason behind discontinuing the previous one. There is evidence that efficacy after switching may be less than with the first TNFi, especially in seropositive patients (Buch et al., 2007, Hyrich et al., 2007, Bombardieri et al., 2007). There is an increasing tendency to switch to a non TNFi biologic after TNFi failure, especially as there are now multiple strategies available (Buch et al., 2012). Several RCTs have been examined efficacy after TNFi failure (Cohen et al., 2006, Emery et al., 2008b, Genovese et al., 2005). Swiss and Swedish registry data demonstrate that in seropositive patients who fail TNFi, switching to rituximab rather than an alternative TNFi leads to better outcomes (Chatzidionysiou and van Vollenhoven, 2013, Finckh et al., 2007).

Targeted Synthetic Disease Modifying Antirheumatic Drugs (tsDMARDs)

Despite the success of biologics, targeting a single cytokine does not completely abrogate the pathology of RA for all patients. Furthermore, being large proteins, biologics have the relative disadvantage of requiring parenteral administration. With advances in understanding of cytokine signaling and small molecular engineering, a question emerged whether targeting intracellular signaling might provide an orally deliverable, safe and efficacious strategy (O'Shea et al., 2013a).

JAK-STAT pathway

Discovery of the JAK-STAT pathway was an important landmark in immunobiology that has advanced our understanding of communication between cells central to host defense. This pathway involves

families of proteins, denoted as JAKs (Janus family tyrosine kinases) and STATs (signal transducers and activators of transcription). The JAK-STAT pathway operates downstream of more than 50 cytokines and growth factor receptors, and it is regarded as a central communication node for the immune system (Villarino et al., 2017). Signalling through the JAK-STAT pathway is initiated when a cytokine binds to its corresponding receptor. This instigates a conformational change in the cytoplasmic portion of the receptor, leading to activation of receptor associated JAK enzymes and phosphorylation of STATs (Kisseleva et al., 2002). Activated STATs then dissociate from the receptor complex and rapidly translocate from the cytoplasm to the nucleus where they bind to the promoters of a wide range of target genes. The JAK-STAT pathway and the therapeutic efficacy of JAK inhibitors in RA will be discussed in detail in chapter 8.1. I have provided a brief introduction below.

Janus Kinase inhibitors

JAK inhibitors (also known as Janus Kinase inhibitors or "jakinibs") are small molecules that block the activity of one or more of the Janus kinase family of enzymes (JAK1, JAK2, JAK3, TYK2) thereby interfering with the JAK-STAT signalling pathway (Kontzias et al., 2012). An important element of JAK function is the pairing of JAK enzymes required for cytokine receptors to transduce their signals. Each cytokine receptor requires at least 2 associated JAKs in order to signal. This may involve identical JAK homodimers (e.g. JAK2/JAK2) or heterodimers (e.g. JAK1/JAK3) (Murray, 2007).

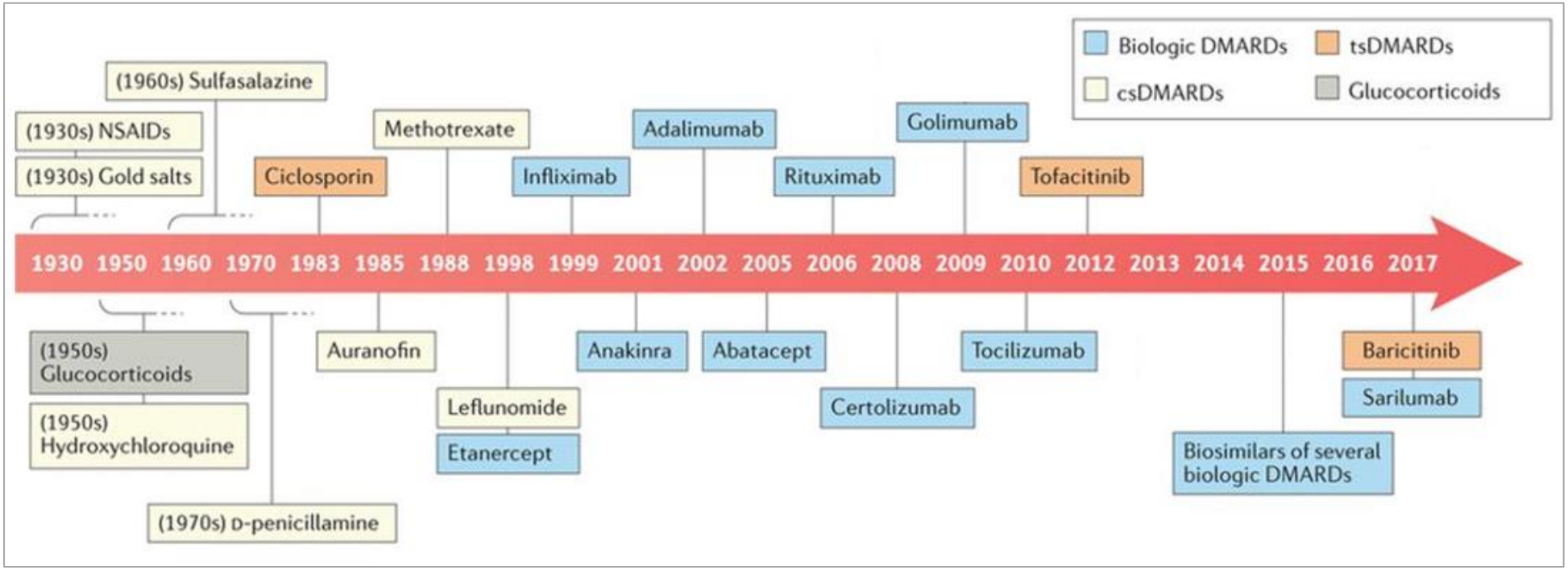
Licensed JAK inhibitors in RA

Tofacitinib became the first JAK inhibitor to be approved for the treatment of RA by the Food and Drug Administration (FDA) in 2012. The European Medicines Agency (EMA) did not approve tofacitinib until 2017 due to safety concerns. Tofacitinib was originally described as a selective JAK3 inhibitor, with 20-fold selectivity relative to JAK2 (Norman, 2014). However, the drug inhibits JAK3 and JAK1, with some

affinity for JAK2 and limited affinity for TYK2. In vitro studies have demonstrated tofacitinib to inhibit γc chain cytokines (IL-2, IL-4, IL-7, IL-15 and IL-21) signalling via JAK3; non-γc chain cytokine signalling including IL-6 mediated by JAK1-JAK2; IFN-γ mediated by JAK1-JAK2; and IL-12 and IL-23 mediated via JAK2-Tyk2 (Scott, 2013).

Baricitinib was approved by the EMA in 2017 at a dose of 4 mg once daily. The FDA approved the 2mg dose in 2018 but declined approval of the 4mg dose citing safety concerns. Baricitinib inhibits JAK1 and JAK2, and to a much lesser extent TYK2. It is considered a JAK3 sparing agent with 100-fold selectivity for JAK1 and JAK2, and some activity against Tyk2 [15]. In vitro studies have demonstrated that baricitinib inhibits IFN-γ and IL-6 via JAK1-JAK2, IL-12/23 via JAK2-TYK2 and erythropoietin and granulocyte-macrophage colony-stimulating factor via JAK2-JAK2 (Richez et al., 2017).

Figure 5. The evolution of treatment for rheumatoid arthritis (Burmester et al., 2017a).



This figure illustrates the evolution of therapies available to treat RA. The earliest treatments available for RA included injectable or oral compound (auranofin) of gold salts. The first methotrexate placebo-controlled trials were not performed until the mid-1980s. The first biologics were the TNF inhibitors, with etanercept approved in 1998. This was followed by other biologics including TNFi and non TNFi agents. Biosimilars reached the European market in 2015. The first JAK inhibitor licenced for RA was tofacitinib, followed more recently by baricitinib.

Rheumatoid arthritis within the context of this thesis

To this point, my introduction has summarised RA in terms of its aetiology, pathophysiology, epidemiology, clinical features, diagnosis, prognosis and management. Importantly, RA remains an incurable disease. Despite substantial advances in our knowledge of its pathology and in the development of a range of therapeutic options, not all patients respond, and a considerable number fail to go into disease remission. Furthermore, patients are still at risk of functional decline, reduced quality of life and work disability and continuing to suffer with increased morbidity and mortality. I chose to focus my research on a range of adverse outcomes in RA. This includes a detailed assessment of treatment failure and adverse events.

1.2 Adverse outcomes in rheumatoid arthritis

Over the last 50 years outcomes in RA have dramatically improved with significant shifts in the treatment paradigm. Despite improvements in our knowledge of its immunopathology and a huge armamentarium of effective treatments, patients with RA continue to succumb to clinically important adverse outcomes. These can be considered as treatment failure due to inefficacy and disease flare or adverse events whilst on treatment.

1.2.1 Disease activity in RA

Clinical practitioners and researchers consider three important measures of disease activity when assessing RA. The first reflects current inflammatory activity demonstrated by the number of tender and swollen joints counts and the level of acute phase response reflected by serum markers. The second is radiographic damage from persistent and aggressive disease, which is assessed by radiological scoring methods, for example the van der Heijde modified Sharp (van der Heijde et al., 1999). The third is health-related quality of life, which is reflected as a composite of several dimensions of health consequences, including pain, physical functioning, stiffness, mental health, social functioning, fatigue and sleep disturbances (Kvien and Uhlig, 2005).

Measuring disease activity with the Disease Activity Score in 28 joints (DAS28-ESR)

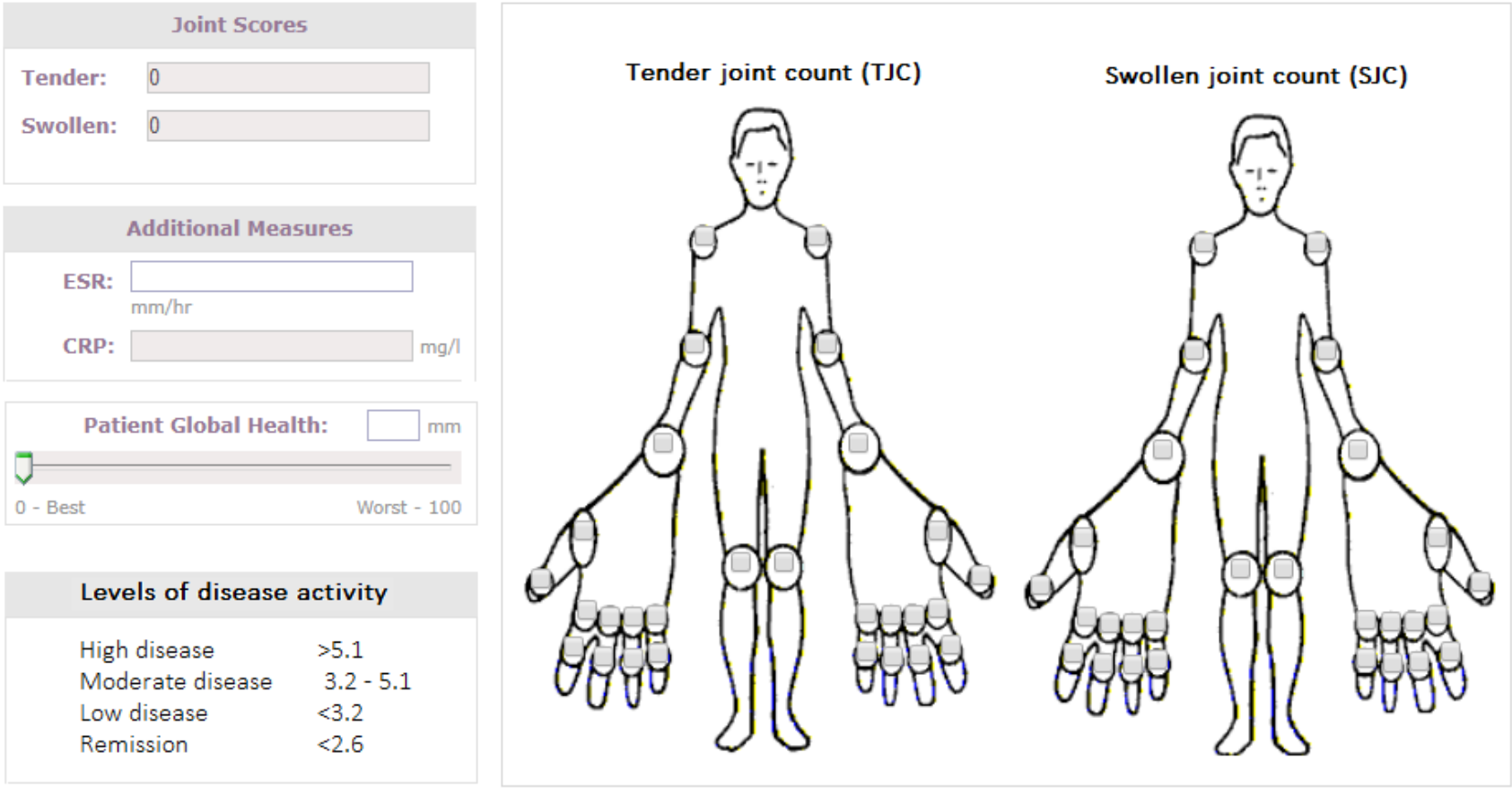
The presentation of RA and its disease course over time is highly variable, both within as well as between individuals. Clinical assessment requires regular evaluation of inflammatory activity. To overcome heterogeneity in assessing disease, composite activity measurement tools have been developed. The first of these was reported in the 1950s and have evolved ever since (Lansbury, 1956). In 1990, the Disease Activity Score in 28 joints (DAS28) was developed using a large prospective study.

Levels of disease activity were equated with the rheumatologist's decision to start csDMARD or stop treatment because of disease remission (van der Heijde et al., 1990, van Gestel et al., 1998). The DAS28 has been validated in its ability to discriminate levels of disease activity and assess treatment response (Prevoo et al., 1995). It is now the most used score in daily practice and is employed by NICE guidelines to established levels of disease activity above which they would advise escalation of therapy.

The DAS28-ESR consists of four variables; 28 Tender Joint Count (TJC), 28 Swollen Joint Count (SJC), ESR and patient's global assessment of disease activity (VAS) (range 0-100) (Figure 6). It uses the square-root and natural log transformation to provide a Gaussian distribution with a continuous scale ranging from 0-10. The level of disease activity can be interpreted as high >5.1, moderate 3.2-5.1, low <3.2 or in remission <2.6. An alternative formula has been developed which incorporates CRP instead of ESR. This has been validated in early and established disease (Hensor et al., 2010, Wells et al., 2009). The correlation coefficient between DAS28-ESR and DAS28-CRP is very strong, although threshold values were found to be lower with DAS28-CRP (high >4.1, moderate 2.3-2.7, low <2.3) (Inoue et al., 2007).

The DAS28 does have several drawbacks. Firstly, the joints of the ankle and feet are not included which at the individual patient level may lead to misclassification. Secondly, each component of the DAS28 is weighted and converted in the formula. The TJC has a weight of 1.95 times that of an SJC, and as square roots are applied this places greater significance on the TJC. For example, a TJC of 3 contributes more to the DAS28 than a SJC of 7 (Jacobs et al., 2014). Thirdly, concomitant fibromyalgia may result in a high DAS28 driven by its positive association with the VAS global and TJC, and not as a reflection of active RA (Ton et al., 2012). Lastly, the ESR is a nonspecific marker which is elevated in numerous conditions including anaemia and obesity. Due to its log conversion, changes in the lower range of the ESR can significantly influence the overall DAS28 score (Jacobs et al., 2014).

Figure 6. Disease Activity Score in 28 joints (DAS28-ESR)



This figure illustrates the four variables; 28 Tender Joint Count (TJC), 28 Swollen Joint Count (SJC), ESR and patient's global assessment of disease activity (VAS) (range 0-100) used to calculate the DAS28-ESR. It uses the square-root and natural log transformation to provide a Gaussian distribution with a continuous scale ranging from 0-10. The level of disease activity can be interpreted as high >5.1, moderate 3.2-5.1, low <3.2 or in remission <2.6.

Measuring health-related quality of life

RA exerts a substantial impact on physical function, which is not directly assessed by the DAS28. Specific instruments have been designed to help measure physical function and operate as indicators of RA disease activity. These tools are developed for generic use and more often employed in clinical trials as patient reported outcomes (PROs) rather than in daily practice.

The Health assessment questionnaire disability index (HAQ-DI) is an RA disease specific questionnaire, self-administered by the patient. It was developed in 1980 and used in most RA clinical trials and observational studies. The HAQ-DI has been validated in numerous disciplines and possesses face and content validity (Bruce and Fries, 2003, Wolfe et al., 2004). In RA, it has been shown to predict mortality (Wolfe et al., 2003), work disability (Wolfe and Hawley, 1998), joint replacement and medical costs (Wolfe and Zwillich, 1998). Each question assesses the amount of difficulty in performing routine activities on a scale ranging from 0 (without any difficulty) up to 3 (cannot be done at all). Four domains relate to dexterity (dressing, eating, reach and grip) and four to mobility (rising, walking, hygiene, and errands and chores). The total score is between 0 and 3 in 0.125 increments. An increasing score indicates worse functioning. Minimal clinically important differences have been published at 0.22, although estimates range widely (0.07–0.87) depending on the population and construct used (Maska et al., 2011). An important limitation of the HAQ score is the floor effect, demonstrated in 10% of patients who cannot improve in score despite clinical improvement. Additionally, the reversibility of the HAQ-DI decreases with increasing disease duration and the score may indicate irreversible joint damage despite suppression of RA rather than active disease (Aletaha et al., 2006).

The short form (SF)-36 (SF-36) is another patient reported outcome designed to assess quality of life (Ware and Sherbourne, 1992). It is not disease specific for RA. The questionnaire comprises 36 items

organised into 8 domains; physical function, physical role, general health, bodily pain, mental health, social function, vitality/fatigue, and emotional role, which are summarized into a physical and a mental component score. Scores are obtained via summation and transformation of item values into a scale between 0 and 100, where higher values represent better health status. The SF-36 is a reliable and valid measure in RA and correlates well with the HAQ-DI (LINDE et al., 2008). The score's subcomponents for physical and mental components are often presented separately and provide insight into the relative changes across these separate domains. As a measure applicable to the general population and patients with other conditions, it is a useful tool for evaluating quality of life across diseases.

Measuring treatment response

Response criteria have been developed to determine an individual disease course and response to treatment. They are also applied to a large number of patients in clinical studies assessing the therapeutic efficacy of certain treatments. The EULAR response criteria incorporate the DAS28-ESR score. Response is defined by i) a degree of change in disease activity and ii) the level of disease activity met. These criteria classify patients as good, moderate or non-responders (van Gestel et al., 1996) (Figure 7).

Figure 7. The EULAR response criteria

	Level of DAS28		
Change in DAS28	**>5.1**	**<5.1 and >3.2**	**<3.2**
>1.2	Moderate	Moderate	Good
>0/6 and <1.2	None	Moderate	Moderate
<0.6	None	None	None

The ACR criteria consists of seven variables of disease activity; i) TJC, ii) SJC, iii) patent's assessment of pain, iv) patient's assessment of physical function, v) patient global assessment of disease, vi) physician global assessment of disease and vii) CRP or ESR. ACR improvement criteria are defined as either a 20%, 50%, or 70% improvement in the TJC and SJC, as well as at least 3 of the other 5 parameters. These are denoted as achieving an ACR20, ACR50 or ACR70 response. This definition focuses on patient change and not on the absolute state of disease activity. These indices are commonly used in clinical trials. The ACR20 response has been used to discriminates between the efficacy of the target drug and placebo. However, it is not an ideal measure of meaningful change as patients achieving an ACR20 still demonstrate substantial disease burden. Despite the differences between the EULAR and ACR criteria, there is a high level of agreement, with equivalent validity and comparable discriminating potential (van Gestel et al., 1999).

1.2.2 Treatment failure: disease flare

Despite optimal control in achieving low disease activity or remission, patients with RA may still experience transient episodes of joint pain, swelling, stiffness and fatigue indicating increased inflammation. These episodes are classified as disease flares. Flares in RA are increasingly relevant. They have become key outcomes in clinic trials, particularly in patients who have attained low disease activity levels or are tapering down or stopping of therapy (Kuijper et al., 2015). Flares can be severe and debilitating and have important implications on long term outcomes.

Flare was defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group as a cluster of symptoms of sufficient duration and intensity to require initiation, change or increase in therapy (Bingham et al., 2009). However there is no agreed construct of what constitutes a flare (ALTEN et al., 2011b), and the frequency of flares reported in clinical practice and research vary depending on

the criteria used to assess them. There are several published DAS28-based flare criteria, the most discriminating and valid is an increase in DAS28 >1.2 or an increase >0.6 if DAS28 ≥3.2 (van der Maas et al., 2013). In clinical practice disease flares are often under recognized, with vast differences in perspective and expectation between patients and clinicians. Qualitative studies reporting on patients' definitions of flare describe events as either 'contained by self-management' or 'uncontrollable prompting a request for medical help'. Clusters of symptoms include 'physical, systemic, emotional and cognitive' with intense, persistent pain a key feature (Hewlett et al., 2011).

Multiple studies have evaluated outcomes in patients who flare. In the short term, flare events are associated with pain, stiffness and loss of functional ability. Their unpredictable nature disrupts family and occupational roles (Morris et al., 2008). In the long-term, patients who flare have more active disease, inferior functioning and worse quality of life outcomes (Saleem et al., 2012). Flare associates with radiographic progression in a dose–response with the number of flares over time (Saleem et al., 2012, Markusse et al., 2015a, Ometto et al., 2016). Furthermore, substantial cardiovascular damage can accumulate during a flare event, contributing to long-term RA morbidity (Myasoedova et al., 2016a). In clinical practice, flare events are often managed with treatment intensification. It may be argued that if a flare event were to spontaneously resolve, the risk of overtreatment may be less serious than the risk of under treatment resulting in long-term disability and joint damage (Saleem et al., 2012).

1.2.3 Treatment failure: primary and secondary failure

Despite major advances in the management of RA, a significant number of patients fail to respond to treatment. Treatment response can be categorized into primary failure (inefficacy; a lack of efficacy since drug initiation) or secondary failure (acquired therapeutic resistance; loss of efficacy over time). Complete absence of treatment response is rare, whilst a partial or inadequate response is more

common. Patients may also fail treatment due to ineffectiveness from non-adherence, drug intolerance or an adverse event. This will be considered separately.

It is well recognised that failure to respond to treatment is associated with worse clinical outcomes. If RA is left untreated or remains unresponsive to therapy, uncontrolled inflammation persists leading to progressive joint destruction, physical impairment, work disability and a significant economic burden. Real world data from the US reported that patients who had not responded to initial bDMARD and tsDMARD experienced higher all-cause and RA-related medical costs and higher indirect costs from medically related absenteeism and days of work lost (Strand et al., 2018).

Primary therapeutic inefficacy

Primary inefficacy is seen with csDMARDs, bDMARDs and tsDMARDs, although much of the literature in this area has focused on biologics. In the early TNFi RCTs 50-70% of patient achieved an ACR20 response with a significant proportion of patients not responding at all. Analyses of observational cohorts report similar figures, with approximately one-third of patients not demonstrating an improvement despite 6 months of TNFi therapy. Only 18% of patients achieved a good EULAR response and 9% of patients were considered to be in remission (Hyrich et al., 2006b). These therapeutic failure rates are not limited to TNFi, with similar frequencies reported with other biologics (SOLIMAN et al., 2012). A study from the US estimated the real-world prevalence of inadequate response to initial bDMARD and tsDMARD therapy at 66% (Strand et al., 2018). With considerable availability of different biologic agents this can lead to patients cycling through medications. The estimated prevalence of multidrug resistant RA (also defined as persistent or difficult-to-treat RA) ranges from 5% to 20% depending on the criteria used (Kearsley-Fleet et al., 2018).

Early studies have attempted to identify patient characteristics which predict treatment response. Improved response to biological therapy was seen with concurrent methotrexate. A lower response rate was associated with females, smokers, longer disease duration, increased levels of disability and a higher number of previously failed csDMARDs (Kleinert et al., 2012, Abhishek et al., 2010, Anderson et al., 2000). However, the cumulative strength of these individual factors in identifying responders is poor (Hyrich et al., 2006b). More recent studies have attempted to identify laboratory predictors of response. It is acknowledged the underlying RA immunopathology may differ between individuals, with distinct synovial membrane infiltrates, cytokines profiles and gene expression (Humby et al., 2019). Plausible biomarkers include CRP, RF and ACPA positivity and low type I IFN gene expression (Lequerré et al., 2019). However, these are not sufficiently sensitive when used alone to predict the treatment response and require confirmation in independent studies (Lequerré et al., 2019).

Drug survival and secondary failure

Drug survival is defined by how long a patient stays on a given therapy. It can be interpreted as a composite measure of effectiveness, safety and tolerability. The largest reason for discontinuation with of RA therapy is inefficacy (Du Pan et al., 2009). Secondary failure with acquired therapeutic resistance is most frequently reported with bDMARD. This may be explained by the formation of anti-drug antibodies (ADA) generated as a consequence of an immune response to the protein base agent, potentially neutralizing its therapeutic effect. ADAs prevent drug molecules from binding to the target cytokine, and correlate with reduced biologic drug concentrations, diminished therapeutic response and treatment discontinuation (Keiserman et al., 2014). Immunogenicity may be more common with mAbs than the soluble receptor fusion proteins. Drug survival is also influenced by poor drug adherence, driven by side-effects profiles, cost, convenience and access.

A systemic review of TNFi estimated 12-month drug survival of 70% and 24-months between 57%-63% (Emery et al., 2019). Drug survival within the TNFi class was reportedly highest with etanercept (Emery et al., 2019, Ebina et al., 2018, Du Pan et al., 2009). Amongst all biologics, abatacept and tocilizumab demonstrate the highest retention rates (Ebina et al., 2018). Several studies have demonstrated that discontinuing a prior biologic may predict lower drug survival with subsequent agents. When used in the second-line setting, drug survival at 12 months and 24 months for TNFi drops to 55% and 40% respectively (Emery et al., 2019). Drug survival rates differ between TNFi and non-TNFi therapy with a higher probability of continuing a non-TNFi agent after TNFi failure owing to using a drug with a different mechanism of action (Favalli et al., 2014, Wilke et al., 2017).

Drug survival is also shaped by other factors including the characteristics of the patient population and the number of available treatment options, which have both changed over time (Hyrich et al., 2011, Simard et al., 2010). Data from the USA and Europe have reported decreasing TNFi drug survival over the last 20 years, whilst data from the UK have demonstrated relative stable rates (Yazici et al., 2009, Hyrich et al., 2011). Finally, a proportion of patients will achieve remission and wish to reduce their drug exposure. This is reported more frequently with the TNFi mAb and does influence overall drug survival, although infrequent during the first 12-24 months of therapy (Ebina et al., 2018).

1.2.4 Treatment failure from adverse events (excluding infection)

An adverse event is defined as 'any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment' (Edwards and Biriell, 1994). The treatment of RA has been associated with a myriad of adverse events, some of which have received significant attention in the literature. Infection is one of the most important adverse events in RA patients and this is discussed separately.

Conventional synthetic DMARDs and adverse events

csDMARDs are generally well tolerated, although patients do experience common side effects, for example gastrointestinal upset or stomatitis with methotrexate. These medications are associated with abnormalities in liver blood tests affecting 30% of patients commencing therapy. Changes are usually transient and not associated with significant underlying liver injury (Curtis et al., 2010). Severe hepatotoxicity is uncommon. Myelosuppression leading to haematologic abnormalities is also observed. These are managed by dose reduction but may require discontinuation depending upon their severity. Methotrexate is associated with hypersensitivity pneumonitis which occurs with a subacute presentation and is more prevalent in patients with pre-existing lung disease (Kremer et al., 1997, Salliot and van der Heijde, 2009). A small proportion of patients taking leflunomide develop new onset or worsening hypertension. Hydroxychloroquine is associated with retinal toxicity which increases in risk with cumulative dose (Rozman et al., 2002, Marmor et al., 2011).

Biological DMARDs and adverse events

Biologic agents are associated with high rates of adverse events and subsequent treatment discontinuation. Injection site reactions are common, usually mild and generally do not prevent continued therapy. Infusion hypersensitivity reaction do occur with rituximab and infliximab although overall the cumulative incidence is low (Yun et al., 2017). Demyelinating disease has been reported with TNFi but not verified in large observational datasets (Dreyer et al., 2016). No causal relationship exists (except in pre-clinical murine studies), however TNFi are not recommended in established disease. Likewise, case series have reported an association with TNFi and heart failure. The German registry has not demonstrated an increased risk of worsening heart failure, but on the contrary, has reported a beneficial cardioprotective effect from reducing RA inflammatory activity (Listing et al., 2008). Tocilizumab has been associated with lower GI perforations, particularly in patients with a history of

diverticulitis (Strangfeld et al., 2017a). This likely relates to the protective immune function of IL-6 in the intestinal barrier. The drug may also cause dyslipidaemia with an increase in cholesterol and triglycerides (SINGH et al., 2011a), although its cardiovascular safety profile is comparable to other biologics (Castagné et al., 2019).

Significant efforts have been made to assess the risk of malignancy with bDMARDs. Biologics modify immunologic pathways with the potential to alter tumour immune surveillance. RA itself is associated with an increased incidence of haematological malignancies (Askling et al., 2005), cervical cancer (Wadstrom et al., 2016) and non-melanoma skin cancer (NMSC). Although meta-analyses of clinical trial data have reported an increased cancer risk with TNFi, long term observational studies have not confirmed these findings (Askling et al., 2009, Wolfe and Michaud, 2007, Askling et al., 2005, Mariette et al., 2011). The association of lymphoma and TNFi is confounded by the strong association of lymphoma and RA cumulative disease activity (Baecklund et al., 2006). The evidence regarding an increased risk of NMSC amongst patients treated with TNFi is conflicting (Mariette et al., 2011, Wolfe and Michaud, 2007, Chakravarty et al., 2005, Mercer et al., 2012). There is considerably less data regarding the risk of malignancy with the non-TNFi bDMARDs. The absolute risk for cancer is low and comparable across different agents, although risks for specific cancer types including NMSC or those with longer latency have not been excluded (Kim et al., 2019, Wadström et al., 2017).

Targeted synthetic DMARDs (JAK inhibitors) and adverse events

As seen with bDMARDs, a theoretical concern exists regarding the risk of malignancy with tsDMARDs (JAKi). These agents block interferon signaling, a central coordinator in tumour surveillance, and NK cells known for their ability to kill tumour cells (Dunn et al., 2006). Although pooled safety data from trials are reassuring, long term experience is limited and post-marketing surveillance will be essential

in evaluating the malignancy risk (Winthrop, 2017). A potential venous thromboembolism (VTE) signal has been observed with baricitinib, with an analysis of pooled data recorded a high number of VTEs. All patients had multiple risk factors and at longer exposure the rate was comparable between doses (0.5 vs 0.6 per 100 patient years in 2mg and 4mg respectively) (Weinblatt M, 2017, Smolen et al., 2018b), and within the published incidence rate for VTE in the RA population (0.3 to 0.8 per 100 patient years) (Ogdie et al., 2017). More recently, a large US claims analysis evaluated the risk of VTE with tofacitinib compared to TNFi, observing a numerically higher but statistically nonsignificant risk of VTE with tofacitinib (Desai et al., 2019). Continued post marketing surveillance of JAK inhibitors for VTE risk has been recommended. Lastly, an elevated incidence of lower intestinal perforations has been reported (Cohen et al., 2017, Xie et al., 2016) alongside hypercholesterolemia and changes in lipoprotein composition (McInnes et al., 2014). This is analogous to the adverse events profile with tocilizumab suggesting the mechanism may lie in blockade of the IL-6 pathway.

1.2.5 Treatment failure from infection

Infection in RA

Patients with RA have an approximate 1.5–2 times increased age adjusted mortality (Mikuls et al., 2002, Goodson et al., 2002, Wolfe et al., 1994, Sihvonen et al., 2004, Smitten et al., 2008a) with infection one of the top causes (Goodson et al., 2002, Wolfe et al., 1994, Thomas et al., 2003). Mortality from infection is increased 4–6 times that of the general population. The incidence of hospitalised infections is 2-4 times that of age- and sex-matched controls (Doran et al., 2002a, Franklin et al., 2007b), whilst the overall infection rate is 70% higher in RA subjects (Doran et al., 2002a). All types of infections are increased in RA, the commonest foci are the respiratory and urinary tract, skin and soft tissue, and bone and joints (Doran et al., 2002a, Franklin et al., 2007b, Smitten et al., 2008a).

Infections in RA have a considerable impact on the individual and their disease course. Clinician's decisions about treatment are influenced by infective episodes. DMARDs are often withdrawn during an infection, which may result in a flare. Interrupted treatment regimens are associated with loss of disease control leading to increased joint damage (Iguchi-Hashimoto et al., 2016, Markusse et al., 2015b). The financial consequences of infections are significant. In the UK, an infective admission costs up to £6000, placing a major financial burden on the NHS (England, 2016). Interruptions in drug treatment during periods of infection have cost implications, as this may be associated with a reduction in drug efficacy and survival.

The increased susceptibility to infections in RA is likely a combination of disease related immunological dysfunctions, immunocompromising comorbidities, as well the use of potent immunomodulatory drugs. Previous research has addressed clinical and pharmacological predictors. Strong associations exist with increasing age, comorbidity (diabetes, lung and renal disease), smoking status and history of previous infection (Subesinghe et al., 2018). An higher infection risk is seen in patients with active RA (Au et al., 2011, Weaver et al., 2013), severe disease (Hernandez-Cruz et al., 1998, Widdifield et al., 2013, Doran et al., 2002c) or in patients with reduced functional capacity (Doran et al., 2002c, Franklin et al., 2007b, Strangfeld et al., 2011a, Stampfli and Anderson, 2009).

Infection and the immunosuppressive inflammatory state of RA

The current dogma in RA is that infection is a result of the "immunosuppressive" therapeutic agents used to treat the condition. This notion is reflected by national guidelines that recommend temporary withdrawal of therapy in the event of an infectious episode (Ding et al., 2010). However the increased risk of infection in RA has been recognised for over half a century, prior to the advent of csDMARDs, suggesting the disease itself likely plays a key role (Cobb et al., 1953). There is evidence for the

immunologic disturbances associated with RA perturbing host defence against foreign pathogens. Disturbances of both the innate and adaptive immune system are thought to contribute to the increased infection risk. Early studies have not indicated numerical cellular defects e.g. neutropenia or reduction in T lymphocytes to be predictive of infection. Instead, a myriad of anomalies of T lymphocyte function have been described in patients with active RA (Vallejo et al., 2004, Hohensinner et al., 2011, Fujii et al., 2009, Shao et al., 2009, Weyand et al., 2014, Cope, 2002, Koetz et al., 2000) which likely contribute to a functional lymphopenia, with an expanding T cell compartment comprising long-lived, senescent and less clonally diverse T cells. This may render a patient functionally immunocompromised (Yang et al., 2015). An emerging theory of "inflam-aging" is described in elderly people characterised by a chronic inflammatory environment which exhausts the immune system, with marked similarities to the changes seen in RA (Pawelec et al., 2014, Fulop et al., 2013). While these individuals may be highly susceptible to infectious episodes, the patterns of infection do not point to a particular defect in host immunity.

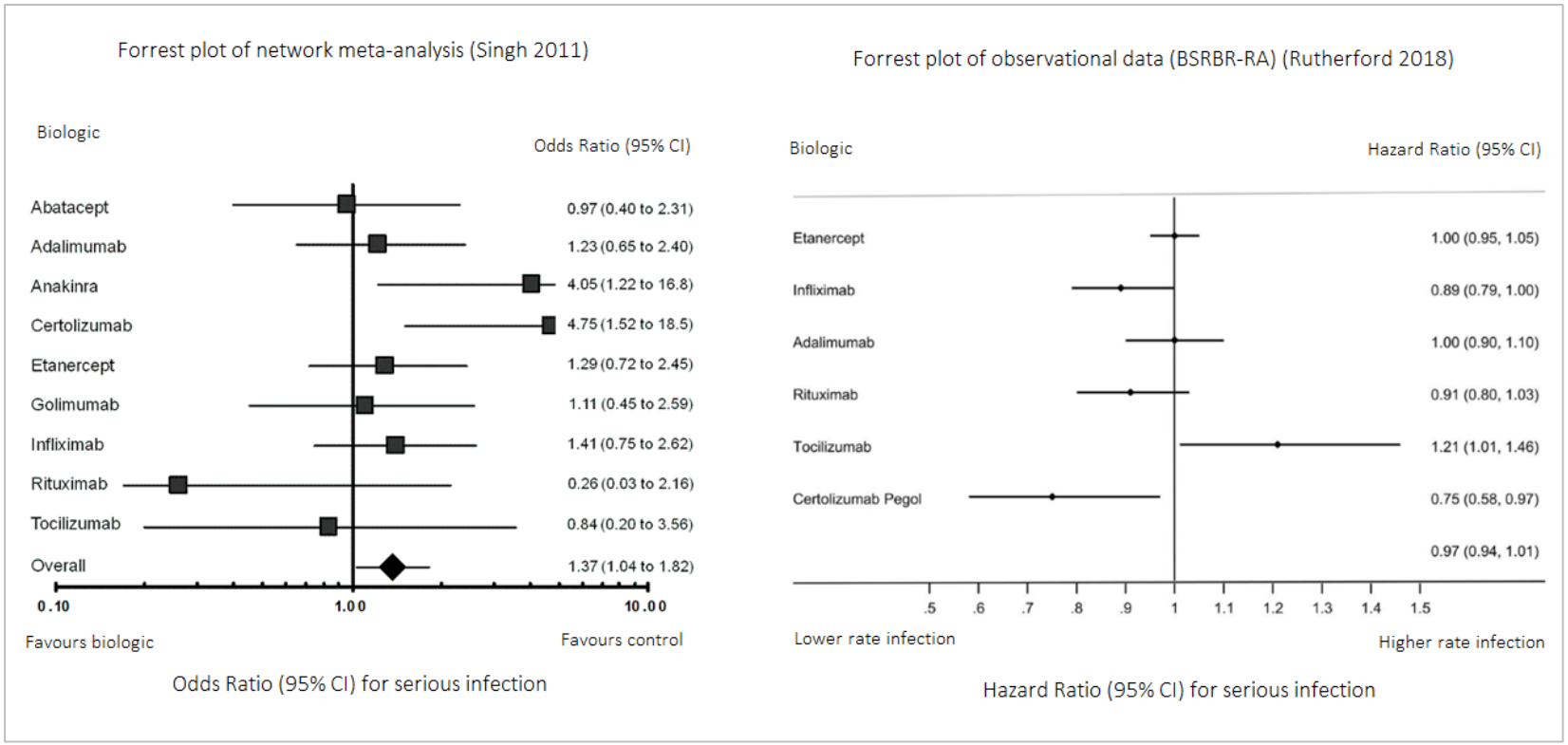
Infection and immunomodulatory drugs

Data on infection risk with immunosuppressive agents are generated from large observational cohorts and national registries. RCTs are generally underpowered to study infection risk. The selective nature of recruitment limits their validity. The risk of infection with corticosteroid therapy is well established, and the magnitude of risk increases in a dose-dependent manner (Wolfe et al., 2006, Greenberg et al., 2010, Dixon et al., 2011b, Dixon et al., 2012). cs-DMARDs have relatively little impact (Lacaille et al., 2008, Doran et al., 2002b, Bernatsky et al., 2007), with reports of a reduction in the risk of milder infection, but no association with serious infections (Lacaille et al., 2008).

For bDMARDs specifically TNFi, registry data have demonstrated a small (~20%) but significant overall risk of serious infection compared with csDMARDs (Galloway et al., 2011, Askling et al., 2007a, van Dartel et al., 2013a, Atzeni et al., 2012, Listing et al., 2005, Curtis et al., 2007, Askling et al., 2007b). This risk is time dependant, being highest within the first 6 months of therapy. This possibly reflects improved disease activity or a healthy user effect with a depletion of susceptible individuals over time (Galloway et al., 2011).

The risk of infection with non TNFi biologics is less well established. A 2011 Cochrane network meta-analysis found that the incidence of serious infection was comparable across biological agents, although certolizumab was found to have a significantly higher rate (Singh et al., 2011b). An analysis of observational data from the BSRBR-RA reported serious infection incidence across bDMARDs, the highest rates reported with tocilizumab and rituximab, and lowest with certolizumab, a direct contradiction to the Cochrane review (Rutherford et al., 2018b) (Figure 8). A subset of patients treated with rituximab develop prolonged hypogammaglobulinemia which may explain the increased infection susceptibility (Barmettler et al., 2018). Abatacept has a risk profile comparable to csDMARD cohorts (Simon et al., 2010) and head to head comparisons to anti-TNF therapy have demonstrated lower rates of discontinuation due to serious infection (Weinblatt et al., 2013). Although differences in risk between bDMARDs are observed, the clinical relevance is greatest in 'high risk' individuals (Rutherford et al., 2018c, Listing et al., 2005, Askling et al., 2007b).

Figure 8. Network meta-analysis and observational analysis of serious infection with biologics (Singh et al., 2011b, Rutherford et al., 2018b)



These forest plots demonstrate the risk of serious infection with biologics. The 2011 Cochrane NMA found that the incidence of serious infection was comparable across biological agents, although certolizumab was found to have a significantly higher rate. An analysis of observational data from the BSRBR-RA reported the highest rate of serious infection with tocilizumab and rituximab, and lowest with certolizumab, a direct contradiction to the Cochrane review.

The Cochrane NMA used indirect comparisons between biologics to estimate the relative risk of infection. Differences in study design and treatment of the control group may have contributed to higher estimates. In the BSRBR-RA analyses it is possible that unmeasured confounders may be responsible for the difference in infection rate. A large proportion of patients receiving certolizumab had were biologic naïve, and sensitivity analyses limiting to patients who had failed a prior biologic did not confirm an advantage of certolizumab compared with etanercept.

JAK inhibition results in the suppression of multiple integral elements of the immune response, and as a consequence, infection represents a major concern. The introduction of JAKi was initially overshadowed by concerns of opportunistic infection observed at higher doses. As the phase III trials have emerged and long-term extension (LTE) data have been evaluated, the absolute risk of serious infections appears comparable to biologics. A safety profile is emerging with viral opportunistic infections the most characteristic infectious complication, specifically the reactivation of varicella zoster virus (VZV) leading to herpes zoster (HZ) (Strand et al., 2015a). These drugs are yet to be examined in observational cohorts and national registries.

Opportunistic infections

Opportunistic infections have emerged as an important complication of targeted therapies in RA. Significant effort has been made to better understand infectious profiles across drug classes. An evidence-driven consensus for reporting in rheumatology clinical trials and surveillance studies has defined a number of organisms as opportunistic (Winthrop et al., 2015a). Important infections to consider with bDMARDs and tsDMARD include tuberculosis (TB), herpes zoster (HZ) and *Pneumocystis jirovecii* pneumonia (PJP).

TNFi increase the risk of both TB and other granulomatous infections. TNFα has a vital role in the formation and maintenance of granulomas (Mohan et al., 2001). The first clinical observation of TB with TNFi was described in an FDA report which noted an increase in TB shortly after initiation of infliximab and suggested likely reactivation of latent disease (Keane et al., 2001). The Spanish BIOBADASER database of patients receiving infliximab before TB screening reported a 20x increased risk ratio compared to non-infliximab patients (Gómez-Reino et al., 2003). The BSRBR-RA reported that mAb TNFi were associated with a three to four fold higher rate of TB compared to etanercept (Dixon et al., 2010a),

The lowest incidence is seen among rituximab users (Rutherford et al., 2018a). More recent analyses from the BSRBR-RA have demonstrated a dramatically fall in TB rates since pre-screening guidelines were introduced (Rutherford et al., 2018a) (Figure 9).

Herpes zoster (HZ) infection involves reactivation of the latent virus in the cranial and dorsal root ganglia. Declining virus specific cell-mediated immunity is associated with the infection. Patients with RA have a 30% higher risk of HZ than non-RA patients (Forbes et al., 2014). Immunosuppression with corticosteroids (Veetil et al., 2013) and DMARDs increases the risk further (Smitten et al., 2007b). Data from the German biologic registry demonstrated a significant increase risk with TNFi mAbs (Strangfeld et al., 2009c), whilst the Spanish registry reported a 10 fold increase in hospitalisation rates due to HZ with TNFi compared with the general population (Garcia-Doval et al., 2010). HZ was the most common opportunistic infection reported in the BSRBR-RA with no difference across biologic class in the rate of serious infections (Rutherford et al., 2018a). As previously discussed, HZ is the most characteristic infectious complication seen with JAKi in RCTs although these drugs are yet to be examined in data from real world clinical practice.

Lastly, there are subtle differences in the rate of *Pneumocystis jirovecii* pneumonia (PJP) between biologics, with the highest incidence observed with rituximab (Rutherford et al., 2018a). This association is well documented in lymphoma treated patients.

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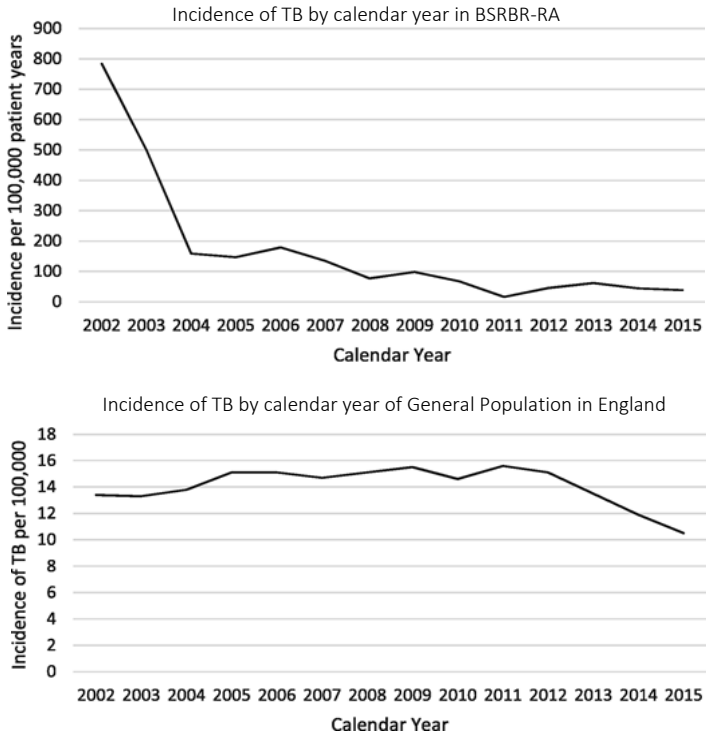
Figure 9. Tuberculosis in patients with Rheumatoid Arthritis (Rutherford et al., 2018b, Dixon et al., 2010a)

A. Incidence of TB by calendar year in BSRBR-RA compared to general population (Rutherford et al., 2018b)



B. Incidence of TB by between TNF inhibitors and csDMARDs in BSRBR-RA (Dixon et al., 2010a)

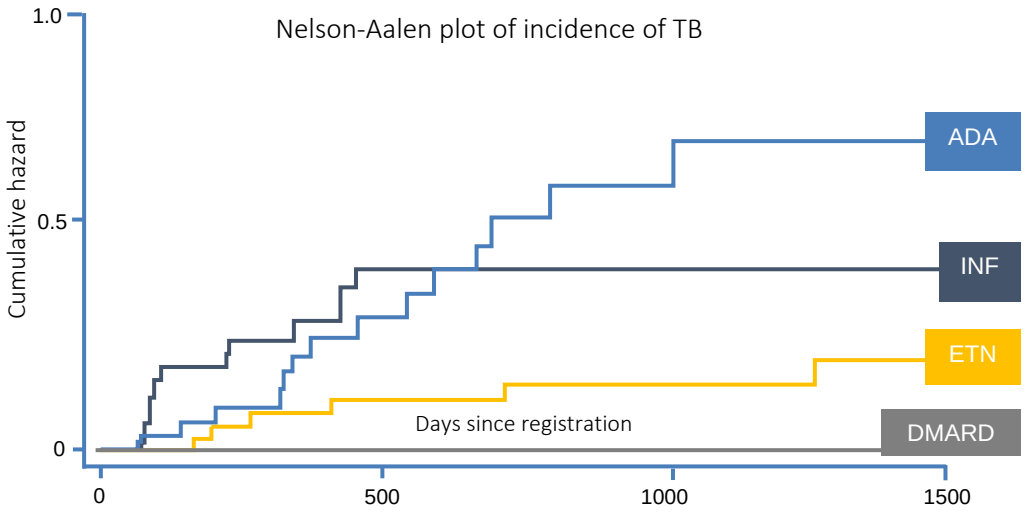


Figure 9A. Analyses from the BSRBR-RA have demonstrated TB rates to dramatically fall since pre-screening guidelines were introduced. A falling rate by calendar year among all biologic users is demonstrated compared to the rate of TB in the general population over the same time period with data provided by Public Health England (Rutherford et al., 2018a).

Figure 9B. The BSRBR-RA reported that mAb TNFi were associated with a three to four-fold higher rate of TB compared to etanercept. The figure demonstrates the cumulative incidence of TB following first exposure to TNFi therapy (Dixon et al., 2010a).

Serious infection and non-serious infections (NSI)

The current classification system for infection in clinical research separates events into serious defined as an infection that is life-threatening or requiring hospitalization or intravenous antibiotics, or non-serious defined as those managed outsides of a hospital admission. This dichotomised classification system is not always helpful and non-serious infections are often disregarded. In RA, serious infections are only the tip of the iceberg. Non-serious infections (NSI) have been reported in 20-30% of RA patients each year (Au et al., 2011, Doran et al., 2002a) and are the most common adverse events in large clinical trials, affecting 25-50% of patients (Dao et al., 2012a). Although these events are not life-threatening, their burden may be high, with recurrent NSI leading to treatment discontinuation (Pan et al., 2009). Despite extensive literature on infection in RA, data on non-serious events are limited.

1.3 Aims of thesis

1.3.1 Adverse outcomes within the context of this thesis

This chapter has highlighted the extensive literature surrounding modern adverse outcomes in RA. I have categorised these into disease flare, treatment inefficacy and adverse events, with a particular focus on infection. In each of these areas, there are key gaps in our knowledge. My interests lie in identifying important predictors of adverse outcomes. The ability to characterise patients who are likely to succumb to these will prove vastly advantageous in clinical practice, ultimately reducing the potential for adverse outcomes and improving disease control, quality of life and long-term health for patients with RA.

1.3.2 Key gaps in the literature

Disease flare: what are the predictors and does flare matter?

Remission and low disease activity are now achievable targets for patients with RA. Our predominant role in clinical practice is ensuring that our patients remain free from symptoms, functional deterioration and radiographic progression. Reducing the frequency and severity of disease flares is paramount. Despite their frequent occurrence, flares have been unrepresented in the research literature. There are few studies that have quantified the frequency of flares events in patients with low disease activity or examined the impact of flare on clinical outcomes (Markusse et al., 2015a, Ometto et al., 2016).

There are little or no data relating to what predicts flare events in patients who remain on stable treatment or those that undergo drug tapering. It has been hypothesised that subclinical inflammation despite apparent remission (determined by remission criteria) may trigger a disease flare (Saleem et al., 2012). Studies have examined the association between power Doppler ultrasound (PDUS) and subsequent flare (Han et al., 2016). Serum biomarkers may detect subclinical disease activity and prove superior to PDUS, with smaller measurement error, less operator-dependence, cost and time. No serum biomarker has yet been defined as predicting disease flare. Functional disability and poor mental health constitute plausible markers for disease flare. Depression correlates with pain and fatigue (Kojima et al., 2009) and is negatively associated with achieving disease remission (Matcham et al., 2018, Michelsen et al., 2017a). Disability has been shown to associated with flare in a small remission cohort (Saleem et al., 2012). Very few studies have evaluated mental health in patients with low disease activity and its role in predicating flare has yet to be determined.

Treatment failure: what are the predictors and does the cause of failure matter?

Treatment failure is distinct from flare. Many patients who experience a flare will remain on treatment. This section considers treatment failure as the situation where a patient stops treatment, requiring a change in therapy. Substantial effort has been made to identify RA patients who are more likely to experience treatment failure. However, there are key gaps in existing literature, including the impact of age, comorbidity and polypharmacy. The efficacy and safety of biologics has been examined in older adults however the results are conflicting with some studies reporting reduced efficacy (Radovits et al., 2009a, Hetland et al., 2010) whilst others have not demonstrated an association (Hyrich et al., 2006b, Filippini et al., 2010), (Genevay et al., 2007). Polypharmacy, the prescribing of multiple drugs for an individual, is rising in prevalence, a consequence of an ageing population with multiple comorbidities,

and advances in therapeutics with guidelines advocating combination therapies. The role of polypharmacy in RA and its association with treatment failure has not yet been examined.

Infection is one of the most important adverse events contributing to treatment failure. Despite extensive literature on infection in RA, there are limited data on non-serious infection (NSI). A meta-analysis of biologics in immune mediated disease found that rate of NSI varied widely across studies (Dao et al., 2012a), reflecting inconsistencies in their reporting. Although these events are not life-threatening their burden may be high. There has been little research into what predicts an NSI and the extent to which immunomodulatory drugs influence this risk. JAK inhibitors are the most recent agents to come to market in RA, and as such their safety profile in terms of both serious and non-serious infections has yet to been examined in the 'real world'. These agents demonstrate unique pharmacokinetic profiles with the possibility of off target effects. A characteristic safety signal is emerging with viral opportunistic infections, notably Herpes zoster. This has received little attention in the literature, and it not known whether this signal may be a 'class effect'.

1.3.3 Overall aims

The aim of my research is to investigate predictors of adverse outcomes in RA. The adverse outcomes that are the focus of this thesis are based on the following specific themes:

(1) Disease flare

(2) Treatment non-response

(3) Treatment related adverse events

Describing the factors that explain these aspects of treatment failure will help rheumatologists make more personalised decisions when treating patients in the clinic.

Aim 1. Defining predictors of disease flare

Objective 1: To define predictors of flare in patients in low disease activity states (Chapter 3).

Objective 2: To define predictors of flare in patients who are in low disease activity or clinical remission undergoing treatment tapering (Chapter 4).

Aim 2. Identifying predictors of treatment non-response

Objective 1: To examine the influence of increasing age on drug survival and treatment discontinuation in patients prescribed biological therapies (Chapter 5).

Objective 2: To examine the importance of co-morbidity and polypharmacy on treatment response and adverse events (Chapter 6).

Aim 3. Treatment related adverse events

Objective 1: To investigate non-serious infections in patients receiving biological therapies (Chapter 7).

Objective 2: To review infection (serious and non-serious) in patients prescribed JAKi (Chapter 8).

1.3.4 Thesis layout and chapter format

The methodology sections of this thesis will introduce the important methods that I have used throughout this body of work. These will be briefly referred to in each relevant results chapter. I will also introduce the important data sources that I have utilised, justifying how each has enabled me to answer the specific research questions posed. The results section of this thesis will address each aim and objective discussed above.

Chapter 2. Methodologies and data sources

2.1 Methodologies

This methodology section is a summary of the different methods and techniques used within this body of research. They are also described briefly within each results chapter.

2.1.1 Systematic review and meta-analysis

Systematic review

Systematic reviews (SRs) are now widely accepted as the most reliable source of knowledge in research. Their objective is 'to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question' (Higgins JPT, 2019). As a tool they minimise bias by using systematic methods that are documented in an advanced protocol and can be easily reproduced and updated as new evidence develops.

The systematic review presented in this thesis (chapter 8: toxicity of JAK inhibition; systematic review and meta-analysis) was conducted in accordance with the preferred reporting items for systematic reviews guidelines (Moher et al., 2015b) and registered with the NIHR international prospective register of systematic reviews. A clear research questions was defined with specified participants, intervention, comparison and outcome variables. Literature search engines employed included MEDLINE, EMBASE and Cochrane Controlled Trials Register databases. These were searched systematically by two investigators with predefined search terms. Abstracts retrieved were screened independently and the

full text of the potential studies for inclusion retrieved and assessed for eligibility. The Cochrane Collaboration's tool was used to assess each studies quality and risk of bias (Higgins et al., 2011a).

Meta-analyses

Pairwise meta-analysis is the statistical method employed to combine results from the relevant studies identified in the systematic review. A summary statistic is calculated for each study to describe the observed intervention effect. A pooled intervention effect estimate is then calculated as a weighted average of the intervention effects estimated in the individual studies. Confidence intervals indicate the precision of the overall estimate obtained (Higgins et al., 2011a).

A pooled intervention effect estimate is then calculated as a weighted average of the intervention effects estimated in the individual studies. Confidence intervals indicate the precision of the overall estimate obtained. Two different models can be employed; a fixed effects model assumes all studies share a common effect size, whereas a random effects model assume that the true effect will vary from study to study (Borenstein). The random effects model accepts the effects being estimated in the different studies are not identical but follow a distribution. The centre of this distribution describes the average of the effects, while its width describes the degree of heterogeneity (Higgins JPT, 2019 , DerSimonian and Laird, 1986). Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect due to random error (chance) alone and is a consequence of clinical and/or methodological diversity among the studies. The chi-squared test assesses whether observed differences in results are compatible with chance alone. The I^2 statistic quantifies the amount of inconsistently in study. This provides the results as a percentage of the variability in effect estimates due to heterogeneity, and ranges from 0%-40% (might not be important) to 75%-100% (considerable heterogeneity) (Higgins JPT, 2019).

The meta-analysis in this thesis calculated crude incidence rates (number of new infections / person-time at risk) for each JAK inhibitor study. Relative risks, a statistic used to describe the risk of an event occurring in the treatment group compared to the placebo group, were estimated using a random-effects Mantel–Haenszel method and expressed as incidence rate ratios with 95% confidence intervals. Incidence rate ratios were compared graphically with forest plots and statistical heterogeneity reported with the I^2 statistic (Figure 10).

Network meta-analysis

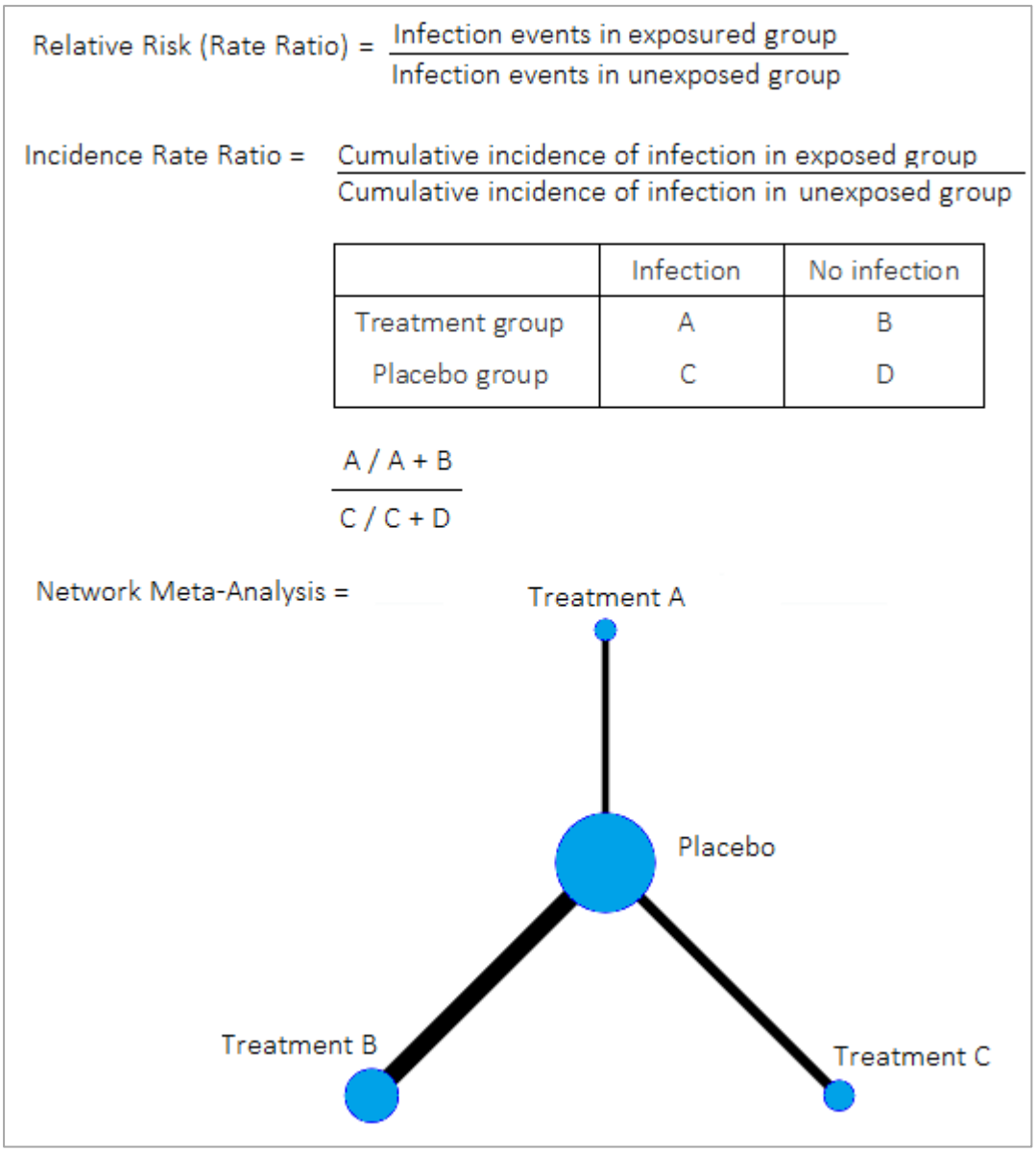
Network meta-analysis (NMA) is an extension of pairwise meta-analysis. It is a method in which treatments can be compared by direct comparisons within a study and by indirect comparisons across studies based on a common comparator. It facilitates the comparison of treatments with different modes of action in a connected network, i.e. as the safety of tofacitinib and baricitinib were compared with placebo in different RCTs, their relative safety of tofacitinib and baricitinib can be estimated indirectly via their common relationship with placebo. Combing direct estimated obtained from pairwise meta-analysis with the indirect estimate from NMA provides a more precise mixed estimate of effect size (Li et al., 2011).

A valid NMA should satisfy the assumption of transitivity, that there are no systematic differences between the studies other than the treatments being compared (Rouse et al., 2017). It should also demonstrate consistent results with pairwise meta-analysis, representing agreement between direct and indirect comparisons. Publication bias must be assessed as unpublished results may occur differentially between treatment groups, impacting overall comparison results.

In this thesis, estimates from the NWA are presented as incidence rate ratios. A network plot graphically summarises treatment comparison. Nodes vary in size according to the number of patients randomised to the treatment. Lines between nodes vary in size corresponding to the number of studies that contributed to the direct comparison (Figure 10).

A probability of treatment superiority can be calculated and reported as a rank according to the surface under the cumulative ranking curves (SUCRA). A SUCRA value of 100% indicates the treatment is certain to be the most effective (or safe) in the network, while a value of 0% indicates it is certain to be the least effective (least safe). SUCRA results should be interpreted with caution, especially if there is heterogeneity in the network, the underlying studies are of poor quality or limited data (Rouse et al., 2017).

Figure 10. Incidence Rate ratios and Network Meta-analysis



This figure illustrates the equation for calculating relative risk and incidence rate ratios, with support of a two by two table. A network plot is displayed to graphically summarise treatment comparison, with nodes that vary in size according to the number of patients randomised to the treatment and lines between nodes that vary in size corresponding to the number of studies that contributed to the direct comparison

2.1.2 Regression models

Regression is used to examine the relationship between a dependent (outcome) and an independent (predictor) variable and allows one to predict the value of the dependent variable using the independent variable. The linear regression model describes a linear relationship. The regression line is a plot of the expected value of the dependent variable for all values of the independent variable. The slope of the regression line (defined as the coefficient) and the intercept (the point on the y axis when the x axis is zero, defined as the constant) are incorporated into the regression equation, with an error term since the regression model is usually not a perfect predictor (Altman, 1991).

Logistic regression is conducted when the dependent (outcome) variable is binary. It requires observations to be independent of each other (not from repeated measurements or matched data) (Rodríguez, 2007). It uses the natural logarithm function to find the relationship between the variables, fitting the data points to provide an 'S' shaped curve to model the data. The curve is restricted between 0 and 1 and demonstrates the probability of the dependent variable being 1 for a given independent variable value. The probability of the dependent variable being 1 is calculated with the odds ratio for a one unit increase in the exposure variable (Figure 11).

The assumptions of different regression approaches require testing, termed ‘model diagnostics’. In linear regression, models can be assessed to test whether relationships are truly linear by plotting the observed versus predicted values or residuals versus predicted values which are a part of standard regression output. If the model assumptions are correct, the points should be symmetrically distributed around a diagonal line in the former plot or around horizontal line in the

latter plot, with a roughly constant variance. If the plot reveals evidence of a "bowed" pattern, it indicates that the model makes systematic errors with unusually large or small predictions.

In this thesis, linear regression has been used to determine the impact of flare on clinical outcomes including disease activity and functional status (chapter 3. predictors of flare; interrogation of the REMIRA cohort). A logistic regression model was employed to examine the relationship between polypharmacy and treatment outcomes in RA, calculating the odds ratio for a predefined 'good treatment response' to biologics by medication count (chapter 6. predictors of treatment non-response; the influence of co-morbidity and polypharmacy). For both analyses, a multivariate model was constructed to assist in identifying likely causal pathways and analyse whether positive or negative associations persist after adjusting for known confounders.

2.1.3 Survival analysis model

The principle of the survival analysis is not simply to look at the relationship between predictors and outcome, but to examine time as an additional outcome. Subjects are followed up over time and observed at which point in time they experience the event of interest. The dependent variable is the time to event and the event status (whether the event of interest occurred or not). Incomplete information about survival time can incorporated into the analysis by censoring of observations. Right censoring refers to either a patient who does not experience the event of interest for the duration of the study or a patient who drops out of the study before the end observation time and did not experience the event. Censoring assumes that the subjects who drop out have the same hazard of an event as those that remain in the study (Altman, 1991).

Survival function provides for every time point, the probability of surviving (not experiencing the event) up to that specified time. The Kaplan-Meier (KM) method estimates survival probability, which is graphically represented on a Kaplan-Meier curves. Hazard function provides the risk that the event will occur per time unit, given that an individual has survived up to the specified time. This is estimated as a hazard rate 'the conditional instantaneous event rate calculated as a function of time' (Altman, 1991).

Cox Proportional-Hazards Model

Cox regression (or proportional hazards regression) (Cox, 1972) investigates the effect of several predictor variables upon the hazard rate. By examining the hazard rate in a group of patients over small increments of time, it is possible to compare rates with another group of patients. The hazard ratio is the ratio of an exponential function of the rates at which patients in the two groups are experiencing events. The null hypothesis would suggest that this ratio is 1 (i.e. event hazard rates are the same in both groups) (Clark et al., 2003). The Cox model is a proportional-hazards model, assuming that the effects of the predictor variables upon survival are additive in one scale and constant over time. Kaplan-Meier and Nelson-Aalen plots can be used to graphically identify this violation by plotting events over time and the cumulative hazard function respectively. If the two lines or curves are parallel, then the hazards can be considered proportional. The Cox model assumes that each variable makes a linear contribution to the model, which is graphically presented using Schoenfeld residual plots against time. If the proportional hazards assumption is true, the residuals will be plotted along a horizontal line demonstrating that they do not change much over time (Figure 12) (Altman, 1991).

Cox regression has been used throughout this thesis to identify predictors of treatment failure from disease flare, treatment non-response or adverse events. Examining time as an additional outcome increases the power of the analyses to reach significant associations, whilst the temporal relationship

between the risk predictor and treatment failure provides scientific insight into the mechanism of the association and clinical insight into risk. Risk is described numerically as hazard ratios with 90% confidence intervals and graphically using cumulative hazard (Nelson-Aalen) plots.

Discrete time survival analysis

Discrete time survival analysis models time in discrete periods during which the event of interest could occur. Data are often the result of interval-censoring, when an event might happen in a continuous range of time but is only observed at discrete moments (Rodríguez, 2007). Applying the complementary log-log transformation allows the survival model to be fitted to discrete survival data, as demonstrated in the analysis of flare in chapter 4. predictors of flare when tapering treatment; interrogation of the OPTTIRA cohort.

Competing-risks regression

Competing risks refers to a separate event occurring impeding the occurrence of the outcome of interest. A patient may suffer from an adverse event leading to the termination of therapy. This removes the patient from the 'risk pool' prior to the actual outcome of interest, for example terminating therapy due to loss of drug efficacy. Unlike censoring, which merely blocks us from observing the event, a competing event prevents the outcome of interest from occurring altogether. It is prudent that analyses adjust for this accordingly. Competing-risks survival modelling is based on the Fine and Gray method (Fine and Gray, 1999) and focuses on the cumulative incidence function. This indicates the probability of the outcome of interest happening before a given time, accounting for the probability that patients may also succumb to a separate event. The cause-specific hazard rate depends on both events of interest (Andersen et al., 2012). This is demonstrated

in the analyses of anti-TNF survival rates (chapter 5. predictors of treatment non-response; the influence of increasing age), where treatment discontinuation is due to inefficacy or an adverse event.

Multiple failure analysis

Multiple failure-time data refers to two or more events occurring for the same subject. Failure times are correlated within cluster (by subject), but this violates the independence of failure time assumption. To account for the lack of independence of the failure times, a random-effect term is used to model unobserved effects shared within the cluster (Cleves). In this thesis, a multi-failure survival model was used in chapter 7. adverse events on biological DMARDs; non-serious infections in the BSRBR-RA, to account for the high frequency of non-serious infective events. These events were consider ordered failures (the second event cannot occur before the first event) and the conditional risk set model was applied, in which time to each event is measured from entry with inclusion of a variable which indicates the failure order (Cleves). In these analyses some of the covariates changed over time, during the follow-up period, for example the number of sequential biologics prescribed. In order to improve estimations, these were analysed as time varying covariates within the Cox model.

Figure 11. Regression equations

Linear regression =

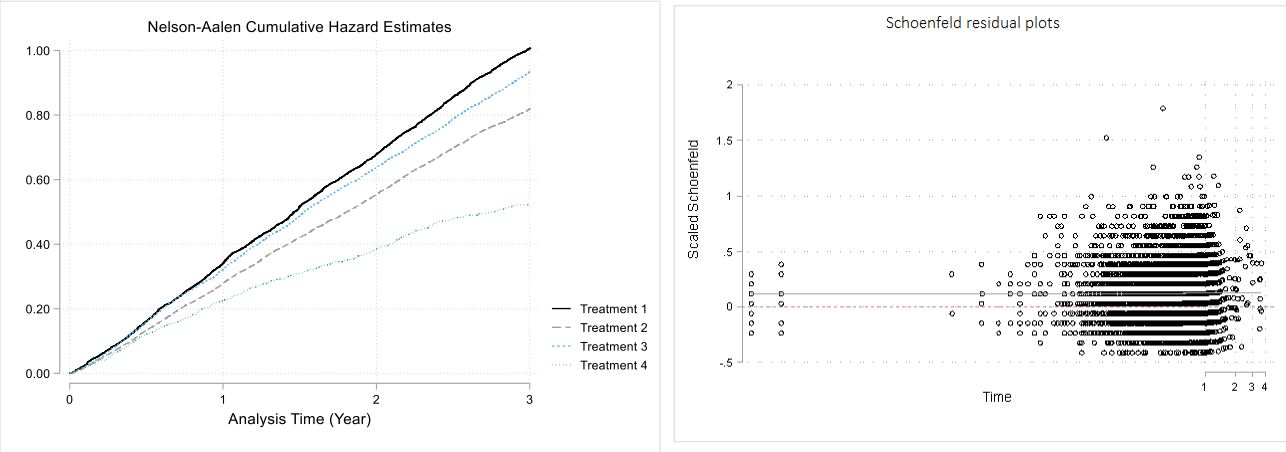
Dependant variable = intercept + (regression slope X independant variable)

Logistic regression

$$\text{Odds ratio} = \frac{\text{probability of an event occurring in a group}}{\text{probability of that event not occurring}} \qquad \text{Odds ratio} = \frac{\pi}{1 - \pi}$$

This figure illustrates the equation for calculating linear regression and logistic regression. For linear regression, the expected value of the dependent variable is calculated by using the intercept (the point on the y axis when the x axis is zero) and the slope of the regression line (defined as the coefficient). For logistic regression the dependent variable is binary, and logit transformation of the dependent variable has a linear relationship with the predictor variables. The probability of the dependent variable being 1 is calculated with the odds ratio for a one unit increase in the exposure variable.

Figure 12. Proportional-hazard model assumptions



This figure illustrates a Nelson-Aalen cumulative hazard plots plotting events over time. If the lines are parallel, then the hazards can be considered proportional. Linear contribution to the model is graphically tested using Schoenfeld residual plots against time. If the proportional hazards assumption is true, the residuals will be plotted along a horizontal line demonstrating that they do not change much over time

2.1.4 Missing data and multiple imputation

Missing data are unavoidable in trials and observational datasets but can potentially undermine the validity of a study's results. Bias from missing data will depend on the reason why the data are missing;

i) Missing completely at random (MCAR): missingness is not related to the person being studied

ii) Missing at random (MAR): missingness relates to the person, can be predicted from other information and is not specifically related to the missing information e.g. males might be less likely to fill in a depression survey, but this doesn't relate to their depression.

iii) Missing not at random (MNAR): missingness is specifically related to the reason it's missing e.g. a patient with depression might be less likely to fill in a depression survey due to severe depressive symptoms.

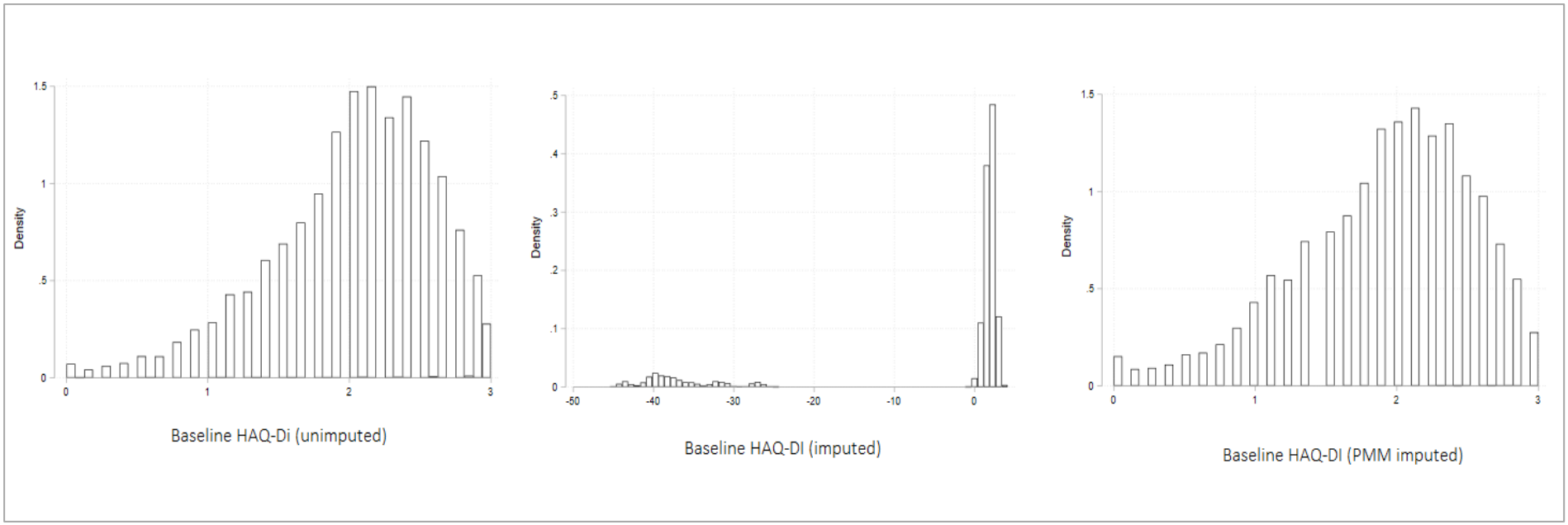
Statistical methods have been developed to deal with missing data. Before employing these methods, it is important to establish the reason for missing data and whether this impacts your predictor or outcome variables. Missing predictor data do not cause bias if the reasons for the missingness are unrelated to the outcome (MAR). Methods to address missing data may lessen the loss of precision and power that would result if you were to exclude individuals with incomplete predictor variables (Sterne et al., 2009). This is also the case when considering missing covariates that are employed in multivariable adjustment. Multiple imputation deals with missing values by creating several different plausible datasets. Missing values are replaced by imputed values, which have been sampled from their predictive distribution based on the observed data. This introduces variation in missing values so the imputed datasets only useful when averaged together to give overall estimated association. To take account of the variability between the imputed datasets, standard errors are calculated using Rubin's

rules. This reflect the uncertainty associated with the missing values (Sterne et al., 2009, Dong and Peng, 2013, Little RJA, 2002).

Important limitations of the imputation model are as follows: when data are missing not at random (MNAR), the multiple imputation introduces bias greater than seen in complete cases analyses. It is prudent to assess for differences in complete cases and multiple imputation results to identify this. To reduce bias further and ensure that the missing at random (MAR) assumption is plausible, it is suggested to include enough variables that may predict missing values in the imputation model (Sterne et al., 2009). There is no established cut-off limit for the percentage of missing data in which one can successfully use an imputation model (Dong and Peng, 2013). However, the face validity of the results will lessen if a high proportion of data are missing. Imputation methods assume that data are normally distributed. Imputing a variable that demonstrates a highly skewed distribution on the assumption that it is normally distributed can produce implausible results. An example of this is the HAQ-DI (Figure 13). Predictive mean matching (PMM) produces imputed values that are much more like real observed values, by borrowing an observed value from a donor with a similar predictive mean. Although if there are few donors in the vicinity of an incomplete value (donor sparsity), the imputed value may lead to bias (Morris et al., 2014).

The observational datasets examined in this thesis had limited missing data and in nearly all analyses, there were complete outcome data. The exception is a component of the polypharmacy analyses which examined treatment response at 12 months, where DAS28 scores were missing for 16% of the cohort (chapter 6 predictors of treatment non-response; the influence of co-morbidity and polypharmacy). There were few missing data on predictor variables and less than 20% missing data on baseline covariates employed in multivariable adjustment. These data were considered missing at random.

Figure 13. Predictive Mean Matching for imputing HAQ-DI



This figure illustrates skewed distribution HAQ-DI data that has been imputed and produced implausible results. Predictive mean matching (PMM) has produced imputed values that are much more like real observed values, by borrowing an observed value from a donor with a similar predictive mean.

Missing value were imputed using multivariate sequential imputation using chained equations. Firstly, all missing values were filled in by simple random sampling with replacement from the observed values. The first variable with missing values, say DAS28, was regressed on all other variables. Missing values in DAS28-1 were replaced by simulated data points drawn from the corresponding posterior predictive distribution of DAS28-1. Then, the next variable with missing was replaced by the same cycle. The imputation included 20 cycles, where at the end of the cycle a single imputed dataset was created and the process was repeated to create 20 imputed datasets. The 20 datasets were combined using Rubin's rules and the combined estimates and standard errors were presented. This is discussed in more detail in each relevant results chapter.

2.1.5 Propensity model

Observational studies differ from randomised control trials where patients are randomly assigned to one of two or more clinical interventions. In contrast, treatment selection in observational studies may be influenced by the characteristics of a patient. For example, it is plausible that patients with a greater risk of adverse events are more likely to be prescribed TNFi monotherapy which is presumed to have a better safety profile than TNF-csDMARD combination therapy. This leads to channelling, a form of selection bias where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences (Petri and Urquhart, 1991). As the baseline characteristics of these two treatment groups differ systematically, one must account these differences when estimating the effect of treatment on outcomes.

Propensity scores are very useful when analysing observational data, enabling the balance of baseline covariates between the two groups of patients being compared. This allows one to analyse non-

randomized data so that it mimics some of the characteristics of a randomized controlled trial (Austin, 2011). The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. It functions by balancing the distribution of measured baseline covariates so that they are similar between two treatment groups. Patients with the same propensity score will have the same distribution of observed baseline covariates and have on average the same potential outcomes. Therefore comparing treated and untreated subjects with the same propensity score gives an unbiased estimate of the effect of treatment (Rosenbaum and Rubin, 1983).

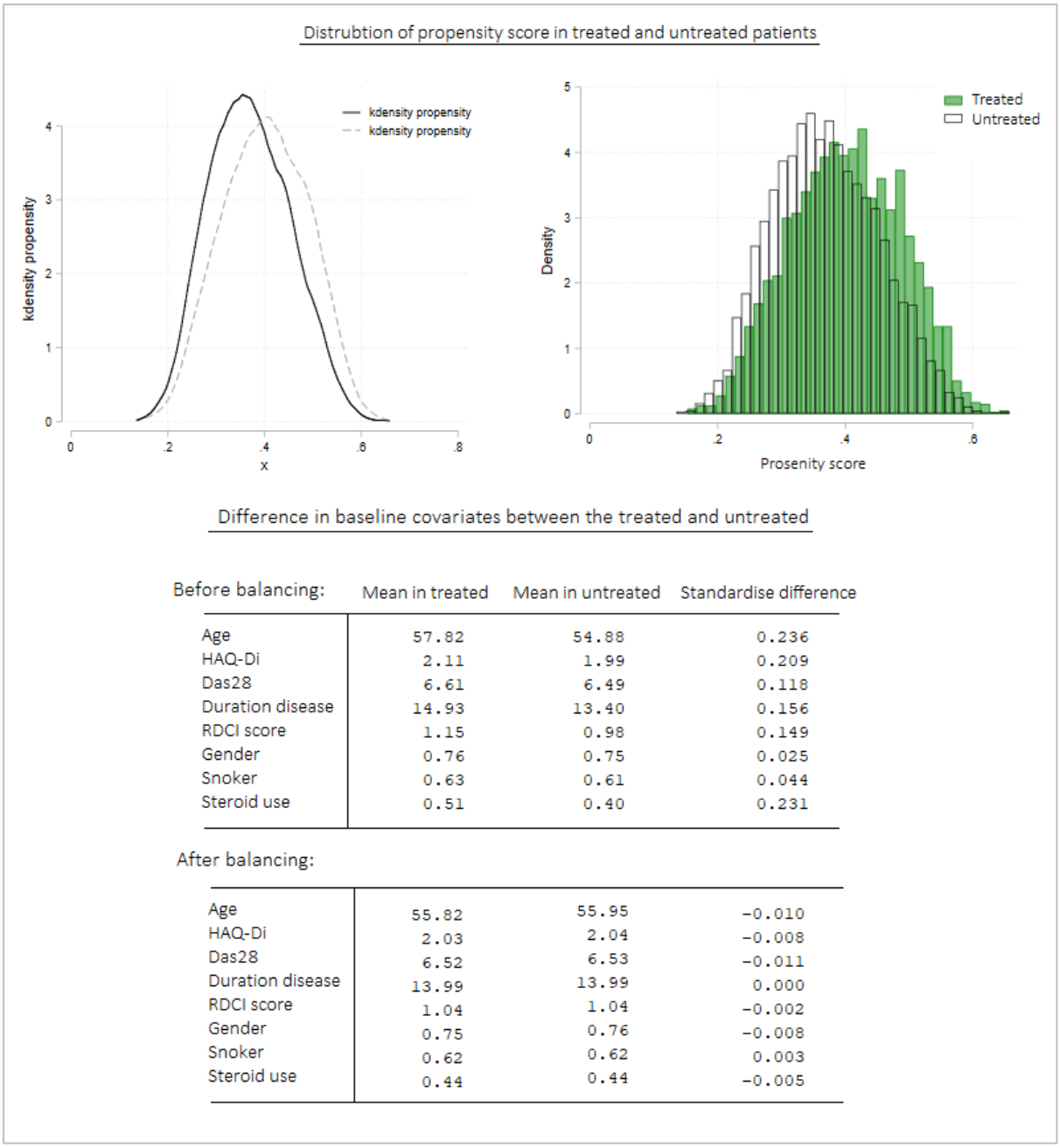
A propensity score (PS) is generated by using a logistic regression model, regressing treatment status on observed baseline characteristics (Austin, 2011). The propensity score is then used to balance covariates using one of three methods: PS matching, stratification on the PS or inverse probability of treatment weighting (IPTW) using the PS. The different methods are effectively estimating the effect in different populations, with different distributions of covariates. (Lunt et al., 2009). IPTW uses weights based on the PS to create an artificial sample in which the distribution of measured baseline covariates are independent of treatment assignment. A patient's weight is equal to the inverse of the probability of receiving the treatment that the patient actually received (Austin, 2011)

Important limitations of the propensity score model are as follows: if crucial variables have been omitted from the PS, the groups may remain unbalanced failing to eliminate bias. In observational datasets one is limited by the variables that have been collected, which may not be sufficient to balance treatment groups. Matching on PS is fairly straightforward if the two groups of patients demonstrate similar scores. However if there is little overlap in PS, a large number of patients will not be matched. This result in fewer subjects being included in the analysis, and those that are included have PS (and baseline covariates) that poorly represent the overall treatment group. Each method available for

balancing patients on their PS has its own limitations and the use of different techniques may affect overall study results and limit reproducibility (Streiner and Norman, 2012).

In this thesis, a propensity score model was used when analysing treatment non response in older adults on TNFi monotherapy compared to TNFi combination therapy with methotrexate (chapter 5. predictors of treatment non-response; the influence of increasing age). A PS was calculated regressing treatment status on baseline characteristics including age, sex, disease duration, DAS28, HAQ, Rheumatic Disease Comorbidity Index (RDCI), smoking status and steroid exposure. IPTW was employed to match patients receiving TNFi monotherapy compared to those receiving TNFi-methotrexate combination (Figure 14). IPTW in particular has been studied extensively in the BSRBR and has been suggested as a robust method in this cohort and will therefore be used in this thesis (Lunt et al., 2009)

Figure 14. Distribution of propensity score and balancing baseline covariates



Difference in baseline covariates between the treated and untreated

Before balancing:	Mean in treated	Mean in untreated	Standardise difference
Age	57.82	54.88	0.236
HAQ-Di	2.11	1.99	0.209
Das28	6.61	6.49	0.118
Duration disease	14.93	13.40	0.156
RDCI score	1.15	0.98	0.149
Gender	0.76	0.75	0.025
Snoker	0.63	0.61	0.044
Steroid use	0.51	0.40	0.231

After balancing:

Age	55.82	55.95	-0.010
HAQ-Di	2.03	2.04	-0.008
Das28	6.52	6.53	-0.011
Duration disease	13.99	13.99	0.000
RDCI score	1.04	1.04	-0.002
Gender	0.75	0.76	-0.008
Snoker	0.62	0.62	0.003
Steroid use	0.44	0.44	-0.005

This figure demonstrates a propensity score that has been generated between two treatment groups. Patient in the treatment arm have a higher propensity score that those in the untreated group. The tables illustrate differences in baseline covariates before and after balancing using inverse probability of treatment weighting (IPTW).

2.2 Data sources

This section provides a summary of the three main observational datasets employed in this thesis. Each data source has its own unique features and has been utilised to answer a specific research question. The studies that have generated this data differ in their sample size, duration of follow-up, recruitment and data collection. They have their own distinct strengths and crucial weakness, that should be acknowledged when interpreting each result chapter.

2.2.1 REMIRA (REMission in RA) dataset

REMIRA (REMission In RA) is a prospective cohort study investigating RA patients with sustained low disease activity (LDA). Patients with RA diagnosed according to the 1987 revised ACR criteria were recruited between 2009 and 2011. To ensure patients had sustained LDA, inclusion criteria comprised stable csDMARD treatment for > 6 months and a DAS28 < 3.2 for at least 1 month. A disease duration of less than 10 years was required to ensure a more contemporary RA cohort. Three centres across south London participated (King's College Hospital, Guys and St Thomas's Hospital and University Hospital Lewisham). Treatment was left to the discretion of the supervising physician.

REMIRA contains extensive clinical, functional, serum biomarkers and imaging data, which were collected every 3 months over a 12-month period on 152 patients. Clinical data include demographics, smoking status, autoantibody status, disease duration and treatment. Disease activity was assessed by the DAS28-ESR. Patient reported outcome measures included the HAQ-DI, SF-36, EuroQol also known as EQ-5D (a standardized instrument which measures health-related quality of life states) and the

Functional Assessment of Chronic Illness Therapy (FACIT-F) (a 13 item questionnaire that assesses self-reported fatigue). Serum biomarker data included 12 protein biomarkers combined into a multi-biomarker disease activity (MBDA) score and a separate biomarker measurement for calprotectin and CXCL10. Ultrasonography of hands and wrists and conventional radiographs of hands and feet were carried out at baseline and 12 months. Ten metacarpophalangeal joints and both wrists were scanned for grey-scale synovial hypertrophy (GSUS) and PDUS.

The REMIRA cohort was utilised to explore the predictive value of a wide range of biomarkers (including clinical, functional, serum and imaging variables) for flare (chapter 3. predictors of flare; interrogation of the REMIRA cohort). The dataset also permitted the exploration of the impact of flare on clinical outcomes. Only patients with sustained LDA were recruited, a population in whom flare is considered to have the greatest impact. The frequency of follow-ups and data collection within REMIRA was superior to that seen in other studies. A major strength is the uniqueness of the cohort. Not only does it provide detailed clinical assessments, but also comprises a large biobank of biological materials which were collected serially over time. This permitted a novel and comprehensive analysis of disease activity biomarkers and their role in predicting flare events. Cross-sectional correlations between disease activity measurements (DAS28 components and serum biomarkers) at time of flare enhanced our understanding of individual flare events and provided an opportunity to characterise these further. Important limitations of the REMIRA cohort include the relatively small study sample size and missing data, particularly with incomplete ultrasound reports. As an observational study, modification in medications were carried out according to the physicians' and patients' choices. Since treatment was not protocolised, this may have impacted on the rate of flare.

There is one prior publication from the REMIRA cohort. This piece of work analysed 2/3rd of the cohort and focused on patients who remained in sustained clinical remission, evaluating the impact on health rated quality of life outcomes (Ma et al., 2017).

2.2.2 OPTTIRA (optimizing treatment with TNF inhibitors in RA study) dataset

OPTTIRA (optimizing treatment with tumour necrosis factor inhibitors in RA study) is a prospective, randomized, open label study investigating TNFi tapering in patients with sustained LDA. Patients diagnosed according to the 1987 revised ACR criteria were recruited from 20 centres across England between 2010 and 2013. They had received TNFi therapy with etanercept or adalimumab for at least 6 months and were taking at least one csDMARD as combination therapy. To ensure sustained LDA patients were only included if they had achieved a sustained good response to therapy with a DAS28 < 3.2 without an increase of > 0.6 for at least 3 months prior. The trial consisted of two phases over a 12-month period. For the first 6 months patients were randomised to a control group which consisted of their constant TNFi dose or to one of two experimental arms, either tapering their TNFi dose by 33% or 66% via increasing dosing intervals. During the second 6-month phase patients in the experimental arms continued to taper their TNFi dose to complete cessation, whilst patients in the control group were randomised to taper TNFi dose by 33% or 66%.

The OPTTIRA dataset contains extensive clinical and functional data collected every 3 months over the 12-month period. Disease activity was assessed by the DAS28-ESR. Patient reported outcome measures included the HAQ-DI, the SF36, the EQ-5D and the FACIT-F.

The OPTTIRA cohort was examined to identify predictors of flare in patients with LDA who are tapering their therapy (chapter 4. predictors of flare when tapering treatment; interrogation of the OPTTIRA cohort). Like REMIRA, the predictive value of a range of biomarkers (clinical and functional) were evaluated. It is acknowledged that the risk of flare is greatest in patients whom tapered or withdraw their RA therapy (Alten et al., 2011a), and as such OPTTIRA provided an exemplary cohort to address this research question. A major strength of the OPTTIRA study was that it was carried out as a clinical trial and thus scrutinised under the more rigorous standards expected for clinical trials. However, the eligibility criteria were pragmatically designed with less stringent inclusion and exclusion criteria than seen in typical RA trials and thus the cohort is more representative than a highly selective clinical trial population. Recruitment was multicentre increasing generalisability. After identifying functional disability to be predictive of flare in the REMIRA analyses, I wanted to test this hypothesis, particularly addressing the role of mental health. OPTTIRA provided extensive functional data mirroring many of the patient reported outcomes collected and analysed in the REMIRA cohort. A major limitation of OPTTIRA is the sample size, which was relatively small with a high non-participation rate, enrolling only 97 patients. Furthermore, sustained flares were not recorded despite evidence that these may be more important than transient flares.

The original OPPTIRA study is published (Ibrahim et al., 2017). The primary outcome was to evaluate whether tapering TNFi doses was associated with a loss of clinical response. In months 0–6 there were 16% flares in controls, 12% with 33% tapering and 29% with 66% tapering. Survival analysis with Cox regression confirmed that compared to constant TNFi dose, tapering by 33% showed no evidence of increased flare but tapering TNFi dose by 66% was associated with flare (adj HR 2.81, 95% CI 0.99 to 7.94 P = 0.051). Combined tapering groups from the initial 6 months and second 6 month phases of the trial demonstrated that tapering by 66% significantly increased the risk of flare compared with 33% (adj HR 3.47, 95% CI: 1.26 to 9.58; P = 0.016).

2.2.3 The BSRBR-RA (British Society for Rheumatology Biologics Register)

The BSRBR-RA (British Society for Rheumatology Biologics Register in RA) is a national prospective observational cohort study. The BSRBR-RA, alongside the German and Swedish Biologics Registers (RABBIT and ARTIS) was one of the earliest pharmacovigilance studies set up specifically to address biologic drug safety in RA. When TNFi therapy was introduced to the UK, the British Society of Rheumatology (BSR) guidelines advised all UK rheumatologists to enrol patients prescribed TNFi onto a national register as an essential part of the prescribing process. Thus, the BSRBR-RA was established in 2001 to monitor the long-term safety of biological therapies. An alliance was formed between the BSR, the pharmaceutical industry and the University of Manchester where the register is held. Patients with RA commencing therapy with a biologic or JAK inhibitor are asked to participate in the register. The design includes the establishment of a comparison cohort of patients with active RA, treated with csDMARDs. Initial BSRBR-RA biologic cohorts were for etanercept and infliximab users. Adalimumab, rituximab, tocilizumab and certolizumab-pegol cohorts were recruited in 2004, 2008, 2010 and 2010 respectively. An abatacept and golimumab cohort have not been recruited. Biosimilars for TNFi and rituximab have been recruited since 2016, whilst JAK inhibitors tofacitinib and baricitinib, and sarilumab have been recruited since 2017/2018.

The BSRBR-RA contains clinical data including demographics, smoking status, comorbidity, autoantibody status, disease duration, details of all previous and current DMARD therapy, and biologic therapy and patient reported outcome measures including the HAQ-DI and SF-36. Follow-up data are collected on a 6-monthly basis for the first 3 years by questionnaires sent to patients and their supervising rheumatology teams, and annually thereafter by questionnaires sent to the supervising rheumatology team only (Figure 15). The focus is on adverse events. Details obtained from the clinical

team include changes in therapy, disease activity measured by the DAS28 and the development of all adverse event whether or not the physician attributes the event to the biologic. Patients are asked to complete a diary recording details of all new diagnoses, new prescriptions and hospital attendances, which are also collected on a 6-monthly basis for the first 3 years. Data on adverse events are also captured by linkage to NHS Digital which provides mortality data.

The BSRBR-RA dataset was employed to evaluate three major components of this thesis, all of which involved patients prescribed biologics: i) the influence of increasing age on treatment non-response (chapter 5), ii) the influence of co-morbidity and polypharmacy on treatment non-response and adverse events (chapter 6), and iii) non serious infections in patients receiving biologics (chapter 7).

The BSRBR-RA was an ideal dataset to explore these research questions.

- Firstly, it is the largest observational data source of patients prescribed biologics within the UK. Importantly the data represent real patients within routine clinical environments. All patients have met NICE thresholds for biologic and JAKi therapy and the results of analyses are directly applicable to the UK RA population.

- Secondly, the BSRBR-RA has collected data on a vastly greater number of patients than would be possible in clinical trials and acquired significant years of patient follow up (currently at >23,500 patients with >222,000 patient years of follow up). This provides great statistical power and permits the detection of signals that may be missed in smaller phase III studies. This is demonstrated by comparing estimates of serious infection risk with TNFi from RCT meta-analyses and the BSRBR-RA. The meta-analysis reported a non-significant odds ratio 1.2 (95% CI 0.89 to 1.63) based upon 6347 patients with 5830 patient years follow-up (Leombruno et al., 2009, Singh et al., 2009) whilst the

BSRBR-RA reported a similar but statistically significant hazard ratio of 1.2 (95% CI 1.1 to 1.5) based upon 15,396 patients with 45,489 patient years follow-up (Galloway et al., 2011). The sample size and length of patient follow up also enables the study of rare outcomes, for example 142 non-TB opportunistic events in 19,282 patients with 106,347 years of follow-up (Rutherford et al., 2018b).

- Thirdly, the BSRBR-RA can directly evaluate risk across agents as the same methodology is used to detect and report on adverse events. In contrast, network meta-analyses rely on indirect comparisons between biologics utilising a common comparator. With differences in trial study design this can introduce error into the comparison. Furthermore, within the BSRBR-RA detailed clinical information is obtained about adverse events which has proved powerful in identifying unusual features. For example, the German registry identified an increased risk of gastrointestinal perforation with tocilizumab. Patients presented without typical symptoms and with lower biomarkers of infection (Strangfeld et al., 2017b).

- Lastly, unlike some other drug registries, the BSRBR-RA has a csDMARD comparator cohort who have active disease on par with patients starting biologics. This has permitted the comparison of the effect of biologic treatment alone on safety signals.

The BSRBR-RA does have certain limitations.

- As an observational study, recording of information tends to be carried out by clinicians rather than investigators. Data entry is performed by non-researchers which can lead to variations in the details recorded and coding. The register is susceptible to missing data and incomplete capture of cases with right censorship, which may affect the interpretation of rare adverse outcomes.

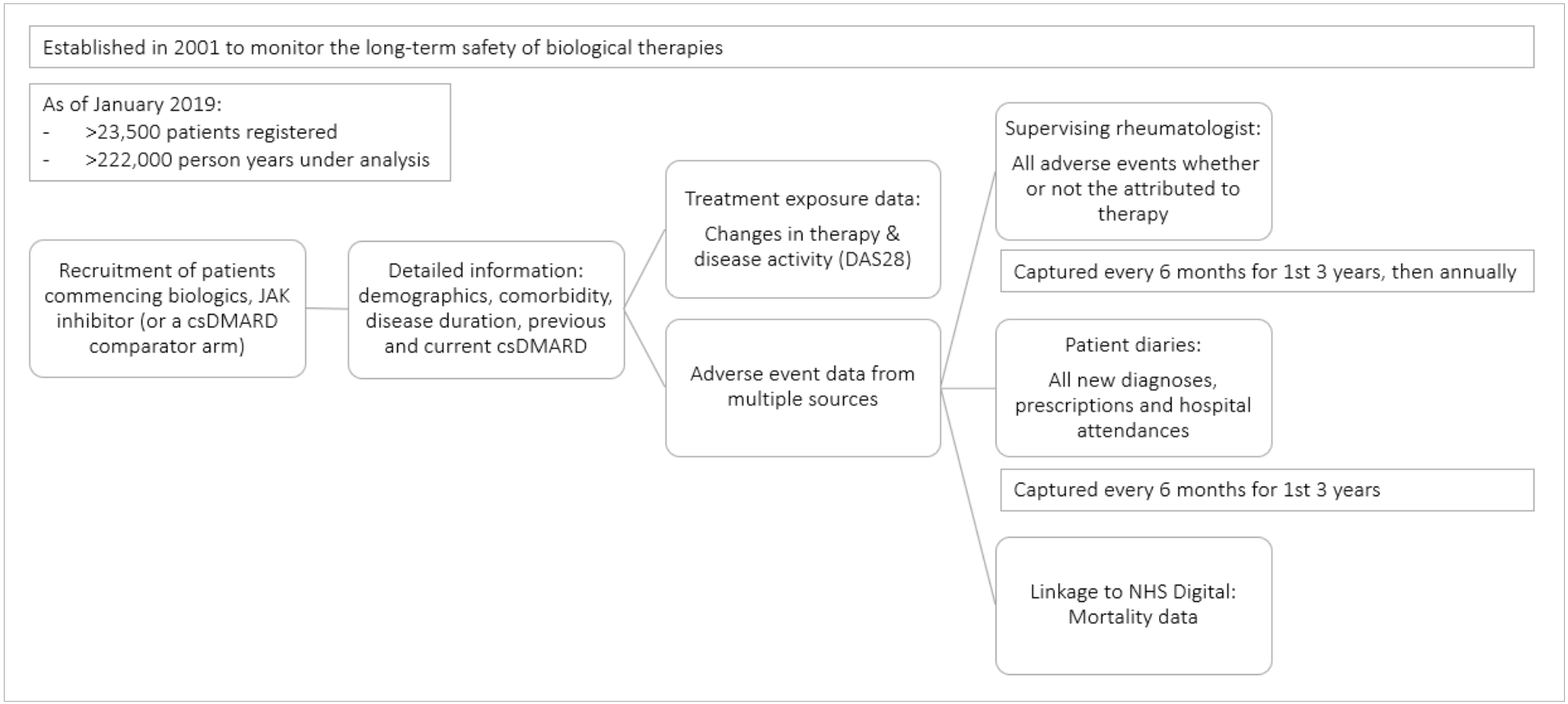
- Secondly, in contrast to RCTs patients in the BSRBR-RA are not randomised into treatment groups. A clinician chooses the most appropriate treatment for his patient. This choice is shaped by numerous characteristics: disease phenotype, comorbidity, drug costs, clinician preference etc. When comparing outcomes between treatment groups it is essential to consider some of these, which may act as confounding variables causing spurious association. Statistical modelling is valuable in addressing this, although a degree of unmeasured confounding inevitably remains. Furthermore, findings from observational drug registry analyses are subject to channelling bias. This occurs when a patient's demographics, degree of illness or prognosis influences treatment decisions and the treatment group they belong to. For example, an early Swedish analysis of lymphoma with TNFi reported an increased risk, whereas a more recent analysis of the data described a reduced risk. The rates of lymphoma vary widely between the two analyses with the later study reporting fair fewer events. This could be explained by channelling bias. Over time concerns regarding lymphoma risk with TNFi increased, resulting in pre-treatment screening and a reduction in the number of high risk patients being offered TNFi therapy (Askling et al., 2005, Geborek et al., 2005).

- Thirdly the BSRBR-RA is vulnerable to selection bias with patient and drug recruitment. Enrolment of patients requires the time and goodwill of clinicians, with greater engagement from research centres with dedicated research staff. These patients may be managed differently from non-research departments, skewing the cohort and reducing generalisability. Furthermore, as times goes on recruitment of patients may reduce as our understanding and confidence in drug safety profiles improves. Drug selection bias may result from restrictions in prescribing, or a complete absence of certain therapies that have not been adopted onto the registrar e.g. abatacept.

- Lastly patients enrolled in the BSRBR-RA can cycle through different treatment options, which provides a huge amount of data of drug survival. However, there is a lack of standardisation in terminating treatment as this reflects clinical practice and is under the influence of selection factors.

Over the last 18 years, a sizeable collection of research has been published from the BSRBR-RA. Several papers have focuses on the effectiveness of biologic use in clinical practice, identifying predictors of therapeutic response (Hyrich et al., 2006b), efficacy after switching therapies (Hyrich et al., 2007, Hyrich et al., 2008) and biologic refractory disease (Kearsley-Fleet et al., 2018). Substantial progress had been made improving our understanding of the safety profile of these agents, reporting on the serious infection risk compared to csDMARDs (Dixon et al., 2006),(Galloway et al., 2011) and between biologics (Rutherford et al., 2018b, Rutherford et al., 2018a) and the association with cancer (Mercer et al., 2012, Mercer et al., 2015, Dixon et al., 2010b).

Figure 15. The British Society of Rheumatology Biologics Register in RA (BSRBR-RA)



This flow chart illustrates data collected from the BSRBR-RA at baseline and during follow-up. As of January 2019, there were >23,500 patients registered with >222,000 person-years of follow up data.

Chapter 3. Predictors of flare; interrogation of the REMIRA cohort

The chapter represents work undertaken during the early stages on my PhD defining predictors of flare in RA patients with LDA from the REMIRA cohort. One-third of the cohort experienced a flare over the 12-month study period. Interestingly, serum biomarkers only modestly correlated with DAS28 at the time of flare, and two-thirds of flare events were not associated with a rise in biomarker. Baseline characteristics that predicted flare included DAS28, ESR, CRP, PtGA, VAS pain, HAQ-DI, and EQ-5D, with the strongest magnitude of association was seen with HAQ-DI and EQ-5D. Patients who flared experienced significantly worse clinical outcomes at 12 months, reflected by higher disease activity, worse functional outcomes, and greater radiographic progression.

3.1 Introduction

Guidelines for the treatment of RA have emphasised a 'treat-to-target' approach with the explicit aim of low disease activity state (LDAS) (Singh et al., 2016b, Smolen et al., 2010)). However, disease activity in RA can fluctuate. Episodic worsening of disease activity, described as "flare", is common. Flare was originally defined by the OMERACT 9 group as a cluster of symptoms of sufficient duration and intensity to require initiation, change or increase in therapy (Bingham et al., 2009). These definitions focused on the more severe end of the flare continuum for evaluation of flares in RCTs. In daily practice, flare can vary in duration, intensity, frequency and manageability (Alten et al., 2011a) with approximately half of RA patients in remission experiencing a disease flare within 2 years (Molenaar et al., 2004). This has important clinical implications because flares in patients with apparently LDAS are associated with

radiographic progression (Welsing et al., 2004, Markusse et al., 2015a), functional deterioration (Markusse et al., 2015a) and worsening cardiovascular comorbidity (Myasoedova et al., 2016b).

Predicting flare is therefore of direct relevance to clinical practice. Saleem et al demonstrated that functional disability (defined by the HAQ-DI score) and USPD positivity at baseline were independently associated with flare in RA patients in remission (Saleem et al., 2012). Furthermore, a recent meta-analysis revealed an association between USPD positivity and flare in RA patients in remission (Han et al., 2016, Filippou et al., 2018).

The finding of PD positivity despite clinical remission provides evidence that flares may be related to incomplete suppression of inflammation. Based on this hypothesis, serum biomarkers may detect subclinical disease activity and consequently predict flare. In contrast to ultrasound, biomarkers may have smaller measurement error and may be less operator dependent, costly and time-consuming. In recent years, the predictive value of the multi-biomarker disease activity (MBDA) score, calprotectin (S100A8/A9) and CXCL10 for treatment response in RA has been investigated. In the DRESS study, baseline MBDA score was predictive of flare and major flare in patients with low disease activity who did not taper treatment (usual care group) (Bouman et al., 2017). To my knowledge, calprotectin and CXCL10 have not been investigated as predictors of flare in patients in an LDAS. Calprotectin was found to be more strongly associated with ultrasound-detected synovitis than ESR or CRP (Nordal et al., 2017) and baseline calprotectin appeared to be predictive of clinical response to methotrexate (Patro et al., 2016). However, its predictive role as a marker of response to biologic DMARDs is conflicting (Nordal et al., 2016), (Choi et al., 2015). CXCL10 was correlated with multiple disease activity measures in early RA (Pandya et al., 2017) whilst elevated baseline levels of CXCL10 were associated with favourable response to TNFi therapy in RA (Han et al., 2016).

The aims of this chapter were three-fold. Firstly, to describe the frequency of flares in a cohort of prospective RA patients in stable LDAS (including remission) over 1 year. Secondly to explore the predictive value of a wide range of biomarkers (including clinical, functional, serum and imaging variables) for flare. And thirdly to evaluate the impact of flare in RA patients with low disease activity states.

3.2 Method

Study design and patients:

The REMIRA study is a prospective cohort study investigating RA patients with stable LDAS including clinical remission. Adult RA patients diagnosed according to the 1987 revised ACR criteria with a disease duration < 10 years, stable DMARD treatment for > 6 months and DAS28 < 3.2 for at least 1 month apart, were eligible for inclusion. Three centres across south London participated: Guy's and St Thomas' Hospital, King's College Hospital and University Hospital Lewisham NHS Foundation Trusts. Patient were managed as part of routine care. The study was approved by the local ethics committee and conducted according to the guidelines of the Declaration of Helsinki (REC:09/H0803/154). Written informed consent was obtained from all patients.

Clinical assessments:

At baseline, demographic, disease and treatment characteristics were collected. Clinical assessments were carried out every 3 months for 1 year and included pain and fatigue (both on visual analogue scale 0-100), DAS28, CRP and ESR. Questionnaires were used to assess function and quality of life: HAQ-DI, EQ5D-3L (EuroQol 5-dimension scale), SF-36: including physical component score (PCS) and mental component score (MCS) and FACIT-F. Flare was defined according to previously validated criteria: a

DAS28 increase of >1.2 compared with baseline or a DAS28 increase of >0.6 compared with baseline and concurrent DAS28 ≥3.2 (van der Maas et al., 2013). For patients with multiple flares, only the first flare was considered in analyses.

Serum biomarker measurements:

Serum samples were obtained at each time point and stored at −80 ^{o}C until being shipped frozen to the Crescendo Bioscience Clinical Laboratory (South San Francisco, CA, USA) for MBDA score, calprotectin and CXCL10 measurement. The MBDA test (Vectra® DA, Crescendo Bioscience) combines the serum concentrations of 12 protein biomarkers (interleukin-6, tumour necrosis factor receptor type I, vascular cell adhesion molecule 1, epidermal growth factor, vascular endothelial growth factor A, YKL-40, matrix metalloproteinase 1, MMP-3, CRP, serum amyloid A, leptin and resistin) in an algorithm to provide a score that quantifies RA disease activity on a scale of 1-100 with validated categories for low (≤30), moderate (30 to 44) and high disease activity (>44) (Centola et al., 2013). Calprotectin and CXCL10 were measured by ELISA (Buhlmann MRP 8/14 ELISA Product Code EK-MRP8/14m; R&D Systems Human CXCL10/IP-10 Quantikine ELISA Product Code DIP100).

Imaging assessments:

Ultrasonography of hands and wrists and conventional radiographs of hands and feet were carried out at baseline and 12 months. Erosive progression was defined as new or larger erosions over 1 year on radiographs. All sonographic assessments were performed using high-sensitivity ultrasound equipment (GE Logiq 9) with a 2D M12L transducer. A single experienced sonographer (TG), blinded to clinical or laboratory data, scanned 10 metacarpophalangeal joints and 2 wrists from a dorsal aspect for grey-scale synovial hypertrophy (GSUS) and intra-articular PDUS (Ohrndorf and Backhaus, 2013). GSUS and PDUS were graded on a scale of 0-3 using a validated semi-quantitative scoring system (Wakefield et al., 2005). The composite GSUS and PDUS scores were the sum scores of the 12 individual joints.

Statistical analysis:

Descriptive statistics were provided with mean (+/− standard deviation (SD)), median (interquartile ranges, IQR) or frequencies depending on data distribution. Cross-sectional correlations between all measurements (biomarkers and DAS28 components) at time of flare were assessed by Spearman's correlation coefficient (r_s), and interpreted according to commonly used classification: r_s<0.20: very weak, r_s=0.20–0.39: weak, r_s=0.40–0.59: moderate, r_s=0.60–0.79: strong and r_s>0.80 very strong correlation (Swinscow, 1997).

To identify predictors of time to flare, I performed univariate Cox regression in which time to flare was the dependent variable and clinical, functional, serum and imaging measurements the independent variables. Multivariate analyses were performed to identify factors that were independently associated with flare, adjusting for age, gender, DAS28, VAS-pain, CRP, ESR and US scores (for HAQ model only) and MBDA score (for EQ-5D model only).

Linear regression was used to determine the impact of flare on 12-month clinical outcomes (i.e. disease activity and functional status). A multivariate linear regression model was applied adjusting for baseline age, gender, disease duration, erosive status, baseline DAS28, HAQ and baseline variable of interest. A P value ≤ 0.05 was regarded as being significant. As this was an exploratory study, no correction for multiple hypothesis testing was performed.

Missing data were addressed using a multiple imputation module. With the exception of ultrasound and EQ-5D, there were few baseline data missing [n=<4, (2.6%)]. Baseline ultrasound data were missing in 49 patients (32% of the cohort), whilst baseline EQ-5D was missing in 17 patients (11.2%). During follow up, in total 12% of data on the components of the DAS28 score were missing; at 3-month n=19 (12.5%); 6-month n=18 (8.8%); 9-month n=20 (13.2%) and 12-month n=15 (9.9%). These data were

considered missing at random. The following variables were used in the imputation model with linear or logistic regression as indicated; disease duration, erosion score, SJC, TJC, PGA, ESR, CRP, RF, ACPA, MBDA score, calprotectin, CXCL10, ultrasound scores, EQ5D, HAQ, FACIT and SF-36. The imputation was run using multiple chained equations with twenty cycles combined using Ruben's rule and the model was compared with complete case analysis. All analyses were performed with STATA 14.1 statistical software.

3.3 Results

Patient characteristics:

In total, 152 patients were enrolled in the REMIRA study. Baseline characteristics are depicted in Table 2. The majority of patients were on DMARD monotherapy (n=70, 46%) and the median (IQR) disease duration was 3 (2-6) years. Ninety-seven patients (66%) fulfilled DAS28 remission criteria (DAS28 <2.6). All patients had synovial hypertrophy (GSUS>1) and 90% had detectable power Doppler activity on ultrasound at baseline.

Characteristics of flare:

Forty-six patients (30%) experienced at least one flare. Twelve patients had first flare by 3 months, 10 by 6 months, 11 by 9 months, and 13 by 12 months. Seventeen patients experienced multiple flares; 11 patients flared at 2 visits, 5 patients at 3 visits and 1 patient at all 4 visits after baseline. When limiting the cohort to patients who were in remission defined by DAS28 <2.6 at baseline, 24 patients of a total 97 (25%) experience at least one flare.

Table 2. REMIRA cohort - baseline patient characteristic

Demographic variables	
Age, years*	57 (14)
Female gender	101 (66%)
Disease duration, years †	3 (2-6)
Clinical variables	
Treatment	
csDMARD monotherapy	69 (45%)
csDMARD combination therapy	59 (39%)
bDMARD therapy	24 (16%)
Prednisolone	3 (2%)
Seropositive (RF and/or ACPA)	103 of 137 (75%)
Erosive	67 (45%)
Tender Joint counts (28 joints) †	0 (0-1)
Swollen joint counts (28 joints) †	0 (0-2)
Patient Global Assessment (mm) †	19 (10-36)
Erythrocyte Sedimentation Rate(mm/hr)†	7 (4-13)
C-Reactive Protein (mg/l)†	5 (1-31)
DAS28-ESR†	2.1 (0.9)
DAS28-ESR <2.6 (remission)	97 of 148 (66%)
Health-related quality of life scores	
Health Assessment Questionnaire score†	0.25 (0-0.86)
EQ-5D score†	0.76 (0.69-1.00)
FACIT Fatigue Scale	42 (34-47)
SF-36 - Physical Component Summary *	46 (11)
- Mental Component Summary *	51 (10)
VAS pain (0-100mm) †	15 (3-34)
Serum biomarker	
MBDA score (1-100) †	31 (18-39)
Calprotectin† (ng/ml)	2358 (1487-3358)
CXCL10† (pg/ml)	198 (143-291)
Ultrasound parameters	
Number of patients with GSUS >0	104 of 104 (100%)
Total GSUS score (/36) †	12 (8-14)
Number of patients with PDUS >0	93 (90)
Total PDUS score (/36) †	2 (1-4)

Data are median (IQR) unless otherwise specified. IQR: interquartile range;

Serum biomarkers at time of flare:

There were 70 individual flares events. Seventeen percent (n=12) of flares were driven solely by increases in PGA and TJC, without any increase in SJC or ESR. In total, 33% of flares (n=23) had a concurrent high MBDA score (>44), whilst 13% (n=44) of visits without flare had a high MBDA score. The levels of ESR, CRP, MBDA score and calprotectin were significantly higher at flare visits than at non-flare visits [median (IQR) ESR 14mm/hr (5-23) versus 6mm/hr (3-12), CRP 5mg/L (5-9) versus 5mg/L (5-5), MBDA 38 (25-50) versus 28 (18-38) and calprotectin 2916ng/ml (2002-4186) versus 2377ng/ml (1504 - 3358)]. DAS28 significantly correlated with MBDA score (rs =0.5, p=0.0002) at time of flare. The rs of 0.5 suggests that the MBDA values explain only 25% of the variation in DAS28. The correlation of MBDA was stronger with the components ESR and SJC, and non-significant for TJC and PGA. Similar findings were seen for calprotectin (rs =0.49, p=0.0007). CXCL10 did not correlate with DAS28 or its components at time of flare (Table 3)

Table 3. REMIRA cohort – the correlation of measures at time of flare in flare group (Rho, p value)

	TJC	SJC	PGA	ESR	DAS28	CRP	MBDA	Calprotectin	CXCL10
TJC	X								
SJC	0.04	X							
	P=0.78								
PGA	0.15	0.06	X						
	P=0.34	P=0.68							
ESR	-0.18	-0.34	-0.11	X					
	P=0.25	P=0.02	P=0.45						
DAS28	0.5	0.54	0.33	0.60	X				
	P=0.0005	P=0.0001	P=0.02	P=0.00					
CRP	-0.04	-0.40	-0.04	0.75	0.48	X			
	P=0.7	P=0.006	P=0.78	P=0.00	P=0.0009				
MBDA score	0.13	0.30	0.003	0.63	0.52	0.75	X		
	P=0.4	P=0.05	P=0.98	P=0.00	P=0.0002	P=0.00			
Calprotectin	0.03	0.31	0.03	0.52	0.49	0.45	0.53	X	
	P=0.84	P=0.04	P=0.86	P=0.0002	P=0.0007	P=0.002	P=0.0002		
CXCL10	-0.03	-0.04	-0.24	0.25	0.05	0.35	0.35	0.28	X
	P=0.87	P=0.82	P=0.11	P=0.1	P=0.71	P=0.02	P=0.02	P=0.07	

Rho, followed by p value

Prediction of flare:

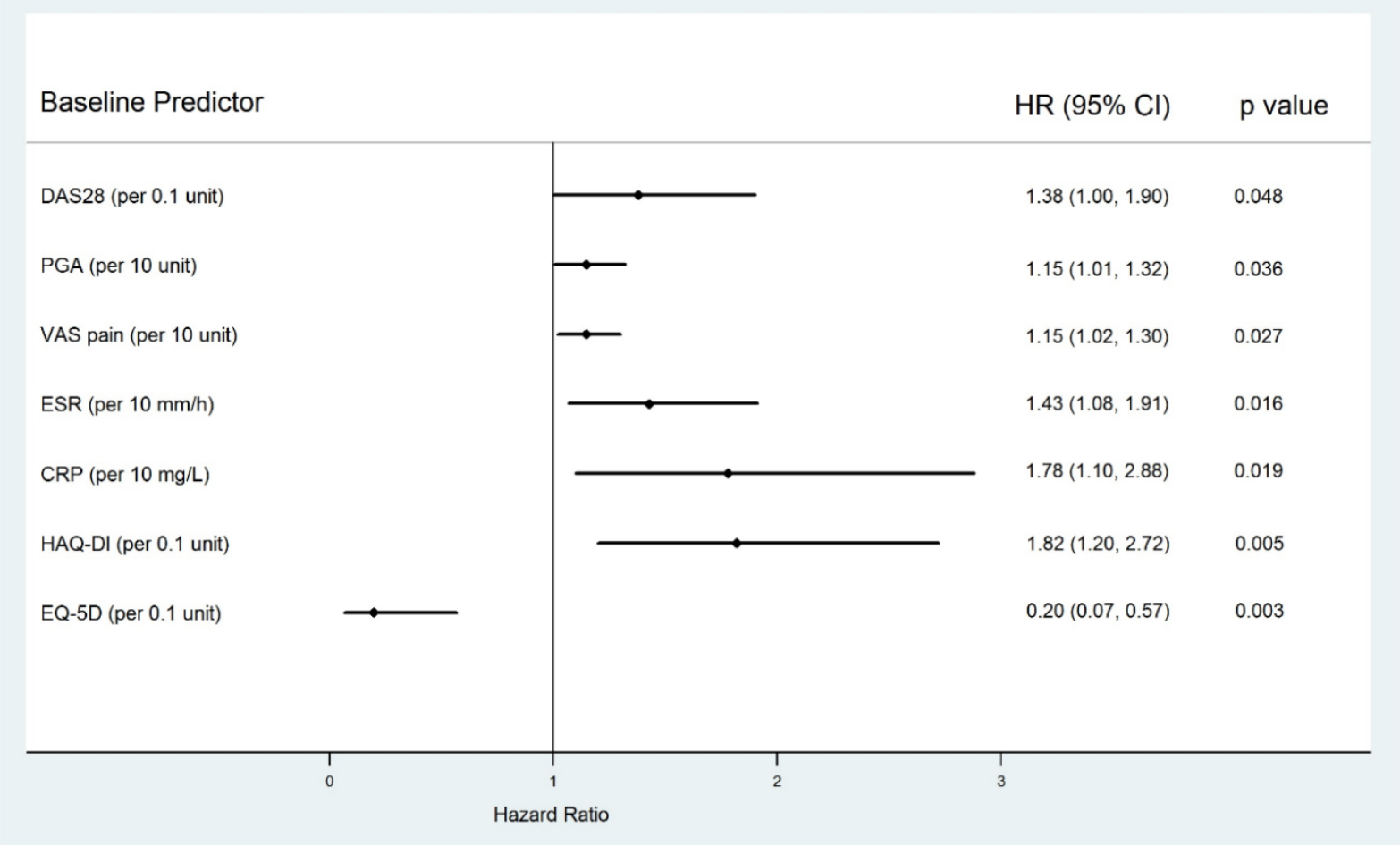
Univariate Cox regression showed that several baseline characteristics were associated with flare (DAS28, ESR, CRP, PGA, VAS pain, HAQ-DI and EQ-5D (Figure 16 and Table 4). The strongest magnitude of association was seen with HAQ-DI and EQ-5D. Baseline ultrasound synovitis (GSUS or PDUS) and mental health (using the SF-36 mental component) were not associated with flare.

Baseline MBDA scores were also not predictive of flare, although a sensitivity analysis limited to flares with a rise in MBDA score to >44 (high disease activity) did show a relationship between baseline MBDA value and flare risk, with each unit rise in baseline MBDA score associated with a 7% increase in flare risk (1.07, 95% CI 1.02 to 1.11; p=0.005) (Table 5). Analysing each component of the MBDA score identified serum amyloid A, leptin and high sensitivity CRP as the strongest predictors of flare. The remaining 9 components of the MBDA score did not individually predict flare.

The imputation model confirmed the association between flare and baseline HAQ-DI and EQ-5D but did not demonstrate any other associations (Table 4). In multivariate analyses only baseline HAQ-DI remained a significant independent predictor of flare [HR 1.76 (95% CI: 1.05 to 2.93) p=0.03].

A final sensitivity analysis identifying predictors of flare was performed limiting the cohort to patients who had DAS28 defined LDAS (DA28 <3.2) or remission (DAS28 <2) (Table 6). As the criteria for LDAS and remission were met, the number of baseline characteristics associated with flare reduced.

Figure 16. REMIRA cohort - forest plot of Cox proportional hazard estimates (95% CI) in univariate analyses examining predictors of flare



This forest plot illustrates baseline variables that predict flare in the univariate analyses. DAS28, ESR, CRP, PGA, VAS pain, HAQ-DI and EQ-5D were all associated with flare. The strongest magnitude of association was seen with HAQ-DI and EQ-5D. A higher HAQ score corresponds to worse quality of life, whilst a lower EQ5D score represents worse quality of life.

Table 4. REMIRA cohort - Cox proportional hazard estimates (95% CI) in univariate, multivariate and imputed analyses examining predictors of flare

	Complete case analysis		Imputation analysis		Adjusted Imputed analysis	
Baseline variables	HR (95% CI)	P. Val	HR (95% CI)	P. Val	HR (95% CI)	P. Val
Age, year	1.00 (0.98 to 1.02)	0.91	1.00 (0.98 to 1.02)	0.95		
Gender, male	1.54 (0.86 to 2.77)	0.15	1.45 (0.80 to 2.61)	0.22		
Disease duration, year	1.04 (0.93 to 1.15)	0.50	1.04 (0.94 to 1.15)	0.41		
Treatment: Ref csDMARD monotherapy						
combination csDMARD	1.22 (0.66 to 2.26)	0.52	1.11 (0.61 to 2.04)	0.73		
bDMARD	0.70 (0.27 to 1.86)	0.48	0.84 (0.34 to 2.11)	0.72		
RF positive	1.27 (0.60 to 2.67)	0.53	1.55 (0.74 to 3.25)	0.24		
ACPA positive	1.74 (0.84 to 3.68)	0.14	1.70 (0.88 to 3.26)	0.11		
Erosive	0.95 (0.53 to 1.73)	0.88	1.22 (0.68 to 2.21)	0.51		
DAS28	1.38 (1.003 to 1.90)	0.048	1.15 (0.85 to 1.56)	0.37	1.00 (0.7 to 1.41)	0.98
TJC28	1.03 (0.88 to 1.21)	0.71	1.01 (0.85 to 1.20)	0.89		
SJC28	0.95 (0.87 to 1.14)	0.56	0.96 (0.80 to 1.16)	0.67		
PGA per 10unit increase	1.15 (1.01 to 1.32)	0.036	1.10 (0.96 to 1.25)	0.17	0.97 (0.84 to 1.12)	0.68
VAS per 10unit increase	1.15 (1.02 to 1.3)	0.027	1.09 (1.0 to 1.20)	0.10	1.09 (0.98 to 1.20)	0.12
ESR per 10unit increase	1.43 (1.07 to 1.91)	0.016	1.16 (0.87 to 1.54)	0.31	1.11 (0.8 to 1.56)	0.53
CRP per 10unit increase	1.78 (1.10 to 2.88)	0.019	1.27 (0.86 to 1.87)	0.23	1.29 (0.77 to 2.14)	0.33
MBDA score	1.01 (0.99 to 1.03)	0.43	1.01 (0.99 to 1.03)	0.25		
Calprotectin	1.00 (1.00 to 1.00)	0.71	1.00 (1.00 to 1.00)	0.49		
CXCL10	1.00 (0.99 to 1.00)	0.85	1.00 (1.00 to 1.00)	0.33		
GSUS score	1.02 (0.95 to 1.09)	0.62	1.02 (0.95 to 1.09)	0.66		
PDUS score	0.99 (0.92 to 1.07)	0.85	1.00 (0.94 to 1.06)	0.94		
HAQ-DI	1.82 (1.20 to 2.72)	0.005	1.61 (1.07 to 2.45)	0.02	1.76 (1.05 to 2.93)	0.031
EQ-5D	0.20 (0.07 to 0.57)	0.003	0.26 (0.09 to 0.74)	0.01	0.68 (0.16 to 2.86)	0.59
SF-36 PCS	0.98 (0.95 to 1.008)	0.17	0.98 (0.96 to 1.01)	0.19		
SF-36 MCS	0.98 (0.95 to 1.00)	0.13	0.98 (0.95 to 1.01)	0.14		
FACIT-F	0.98 (0.95 to 1.00)	0.14	0.99 (0.96 to 1.01)	0.30		

Table 5. REMIRA cohort - baseline characteristics in inflammatory and non-inflammatory flare group and Cox proportional hazard estimates of predictors of flare in high MBDA flare group

	High MBDA flare (n=12)	Low MBDA flare (n=34)
Age, years*	59 (13)	57 (13)
Female gender	7 (58%)	20 (59%)
Disease duration, years †	4 (3-5)	3 (2-6)
Erosive	3 (27%)	17 (34%)
TJC28†	0 (0-1.5)	0 (0-1)
SJC28†	1 (0-2)	0 (0-1)
PGA (0-100mm) †	25 (14-40)	27 (20-38)
ESR†,	20 (9-31)	9 (3-16)
CRP†, (mg/L)	8 (5-17)	5 (5-5)
DAS28-ESR*	2.85 (0.7)	2.20 (1.0)
DAS28 remission	4 (33%)	20 (59%)
VAS pain (0-100mm) †	23 (16-50)	24 (10-47)
HAQ-DI†	0.75 (0.31-0.88)	0.68 (0-1.38)
EQ-5D†	0.74 (0.64-0.80)	0.69 (0.59-0.80)
SF-36 PCS*	48 (11)	44 (12)
SF-36 MCS*	51 (10)	49 (12)
FACIT-F†	40 (31-45)	40 (35-44)
MBDA score (1-100) †	39 (35-50)	25 (17-38)
Calprotectin† (ng/ml)	3038 (2263-4944)	2092 (1479-3215)
CXCL10† (pg/ml)	210 (189-350)	198 (147-266)
Total GSUS score (/36) †	17 (12-19)	11 (9-13)
Total PDUS score (/36) †	7 (4-8)	2 (1-3)

	All flare [n=46 (40%)]		Inflammatory (high MBDA) flare [n=12 (8%)]	
Variables	HR (95% CI)	P value	HR (95% CI)	P value
DAS28	1.38 (1.003 to 1.90)	0.048	2.58 (1.31 to 5.07)	0.01
ESR	1.43 (1.07 to 1.91)	0.016	2.67 (1.63 to 4.37)	<0.01
CRP	1.77 (1.09 to 2.88)	0.019	3.54 (1.90 to 6.58)	<0.01
PGA	1.15 (1.01 to 1.32)	0.036	1.11 (0.85 to 1.44)	0.43
VAS pain	1.15 (1.02 to 1.30)	0.027	1.10 (0.88 to 1.38)	0.38
HAQ-DI	1.82 (1.20 to 2.72)	0.005	1.48 (0.64 to 3.42)	0.34
EQ-5D	0.20 (0.07 to 0.57)	0.003	0.37 (0.44 to 3.17)	0.37
MBDA score	1.01 (0.99 to 1.03)	0.43	1.07 (1.02 to 1.11)	<0.01

Table 6. REMRIA cohort - Cox proportional hazard estimates examining predictors of flare limited to LDAS (DA28<3.2) & remission (DAS28<2.6)

	Original N=152 (flare= 46 patients:30%)		DAS28<3.2 N= 130 (flare= 38 patients:28%)		DAS28<2.6 N= 97 (flare= 24 patients:25%)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, year	1.00 (0.98 to 1.02)	0.91	1.00 (0.98 to 1.02)	0.85	1.02 (0.98 to 1.03)	0.85
Gender, male	1.54 (0.86 to 2.77)	0.15	1.53 (0.80 to 2.92)	0.20	2.17 (0.97 to 4.86)	0.06
Disease dur, years	1.04 (0.93 to 1.15)	0.50	1.05 (0.94 to 1.18)	0.37	1.05 (0.91 to 1.21)	0.47
Treatment (ref: cs DMARD mono)						
- csDMARD comb	1.22 (0.66 to 2.26)	0.52	1.30 (0.66 to 2.58)	0.45	0.94 (0.41 to 2.18)	0.89
- bDMARD	0.70 (0.27 to 1.86)	0.48	0.77 (0.28 to 2.11)	0.62	0.45 (0.10 to 2.01)	0.30
RF positive	1.27 (0.60 to 2.67)	0.53	0.91 (0.47 to 1.74)	0.34	1.60 (1.46 to 5.44)	0.46
ACPA positive	1.74 (0.84 to 3.68)	0.14	2.32 (0.97 to 5.51)	0.06	1.71 (0.62 to 4.71)	0.30
Erosive	0.95 (0.53 to 1.73)	0.88	0.91 (0.47 to 1.74)	0.78	1.15 (0.51 to 2.61)	0.73
DAS28	1.38 (1.003 to 1.90)	0.048	1.53 (0.98 to 2.38)	0.06	1.25 (0.60 to 2.60)	0.54
TJC28	1.03 (0.88 to 1.21)	0.71	1.09 (0.79 to 1.51)	0.60	1.14 (0.77 to 1.69)	0.52
SJC28	0.95 (0.87 to 1.14)	0.56	0.98 (0.80 to 1.20	0.86	1.20 (0.87 to 1.65)	0.26
PGA	1.15 (1.01 to 1.32)	0.036	1.21 (1.04 to 1.41)	0.01	1.24 (1.02-1.50)	0.03
VAS pain	1.15 (1.02 to 1.30)	0.027	1.16 (1.02 to 1.33)	0.03	1.16 (0.97 to 1.39)	0.10
ESR	1.43 (1.07 to 1.91)	0.016	1.47 (1.03 to 2.10)	0.03	1.20 (0.54 to 2.66)	0.65
CRP	1.77 (1.09 to 2.88)	0.019	1.88 (1.14 to 3.11)	0.01	1.69 (0.79 to 3.59)	0.18
MBDA score	1.01 (0.99 to 1.03)	0.43	1.00 (0.98 to 1.03)	0.76	0.99 (0.95 to 1.02)	0.48
Calprotectin	1.00 (1.00 to 1.00)	0.71	1.00 (1.00 to 1.00)	0.30	1.00 (1.00 to 1.00)	0.43
CXCL10	1.00 (0.99 to 1.00)	0.85	1.00 (1.00 to 1.00)	0.24	1.00 (1.00 to 1.00)	0.46
GSUS score	1.02 (0.95 to 1.09)	0.62	1.03 (0.95 to 1.13)	0.49	1.08 (0.95 to 1.23)	0.26
PDUS score	0.99 (0.92 to 1.07)	0.85	0.97 (0.87 to 1.20)	0.70	0.98 (0.83 to 1.17)	0.89
HAQ-DI	1.82 (1.20 to 2.72)	0.005	1.9. (1.19 to 3.15)	0.01	1.96 (0.98 to 3.92)	0.06
EQ-5D	0.20 (0.07 to 0.57)	0.003	0.20 (0.07 to 0.58)	0.00	0.12 (0.03 to 0.58)	0.01
SF-36 PCS	0.98 (0.95 to 1.008)	0.17	0.99 (0.96 to 1.02)	0.36	0.99 (0.95 to 1.03)	0.64
SF-36 MCS	0.98 (0.95 to 1.00)	0.13	0.98 (0.95 to 1.02)	0.29	0.98 (0.94 to 1.02)	0.40
FACIT-F	0.98 (0.95 to 1.00)	0.14	0.98 (0.95 to 1.01)	0.19	0.99 (0.94 to 1.03)	0.60

Outcomes in flare versus sustained remission group:

Adjusting for baseline values, patients who had a flare experienced significantly worse clinical outcomes at 12 months than patients in sustained remission, reflected by higher disease activity, worse functional outcomes and higher radiographic progression scores (Table 7).

Having a flare was associated with a larger than minimal clinically important difference increase in HAQ-DI (β=0.32 (95% CI: 0.29 to 0.36) p<0.01) and EQ-5D (β= -0.11 (95% CI: -0.12 to -0.09) p<0.01). Both the physical and mental performance measures from SF-36 were significantly worse in patients who flared in the unadjusted model. This was more marked with the physical component and did not remain significant with the mental component in the adjusted model. Patients who flared were 3.6 times (95% CI 2.77 to 4.67; p= 0.00) more likely to have erosive progression defined as new or larger erosions over 1 year on radiographs.

Table 7. REMIRA cohort - linear regression model comparing outcomes at 1 year in patients who flare compared to patients who do not flare

		β constant	95% CI	P value
HAQ-DI	Unadjusted	0.59	0.37 to 0.80	<0.01
	Adjusted	0.19	0.04 to 0.32	0.01
	Imputed (Adjusted)	0.32	0.29 to 0.36	<0.01
EQ-5D	Unadjusted	-0.19	-0.26 to -0.13	<0.01
	Adjusted	-0.11	-0.18 to -0.05	<0.01
	Imputed (Adjusted)	-0.11	-0.12 to -0.09	<0.01
SF-36 PCS	Unadjusted	-8.79	-12.4 to -5.18	<0.01
	Adjusted	-3.92	-7.04 to -0.8	0.01
	Imputed (Adjusted)	-5.17	-5.81 to -4.53	<0.01
SF-36 MCS	Unadjusted	-5.42	-9.41 to -1.42	0.01
	Adjusted	-2.86	-6.83 to 1.12	0.16
	Imputed (Adjusted)	-2.94	-3.7 to -2.18	<0.01
FACIT-F	Unadjusted	-7.83	-11.6 to -4.06	<0.01
	Adjusted	-4.07	-7.91 to -0.24	0.04
	Imputed (Adjusted)	-5.09	-5.77 to -4.42	<0.01
DAS 28	Unadjusted	1.32	0.96 to 1.68	<0.01
	Adjusted	1.07	0.77 to 1.37	<0.01
	Imputed (Adjusted)	1.00	0.94 to 1.06	<0.01
		Odd Ratio	95% CI	P value
Erosive progression	Unadjusted	2.33	0.87 to 6.27	0.09
	Adjusted	3.51	1.06 to 11.7	0.04
	Imputed (Adjusted)	3.60	2.77 to 4.67	<0.01

3.4 Discussion

This work was published in *Journal of Rheumatology* in November 2018. In this prospective study, one third of RA patients with LDAS experienced a flare during 12 months follow-up. This is similar to flare rates reported in cohort studies, although these only included patients in remission (Saleem et al., 2012) and in drug tapering studies in patients who remain on stable therapy. In both the DRESS (van Herwaarden et al., 2015) and the POET study (Ghiti Moghadam et al., 2016), the rate of short lived flare was significantly higher in patients who tapered or stopped their TNFi therapy compared to those who continued treatment, although in the DRESS study, the rate of major flares was similar between the two groups.

In this study, I have shown that the occurrence of a flare is hard to predict, but undeniably associated with worse clinical outcomes at 12 months. The study highlights that identification of predictors of flare in patients with LDAS is challenging. In accordance with a previous remission cohort study (Saleem et al., 2012), I found that HAQ-DI, a measure of functional activity, reflected by difficulties in activities of daily living, was predictive for flare. It is plausible that patients with low disease activity and high functional disability are more likely to flare. Functional impairment can herald a flare with the onset of morning stiffness and fatigue. A high HAQ may reflect severe rheumatoid with disease-related damage and the likelihood of grumbling disease.

Serum biomarkers were only modestly correlated with DAS28 at the time of flare. This might be explained by the fact that a flare is defined by worsening of the DAS28 composite score, and an increase in TJC and PGA alone may increase the DAS28 score to a sufficient level to define a flare. It is possible that a flare event is not solely the result of direct synovial inflammation but may be driven by other pathways, for example chronification of pain due to central sensitisation and abnormal regulatory

mechanisms (Schaible et al., 2010). This heterogeneity may partly explain why identifying predictors of flare is challenging. The OMERACT RA flare group recognise the limitation of DAS28 in defining flare events. They are developing a consensus-based core domain set to set to identify and measure flare in RA (Bykerk et al., 2014a, Bykerk et al., 2016). It is likely that improving the definition of flare and establishing a scoring system may help interpret predictors of flare in the future.

I found that a higher baseline CRP and ESR were predictive of flare in the univariate analyses, whilst baseline MBDA score, calprotectin and CXCL10 were not. In the sensitivity analysis limited to flare events with an associated high MBDA score at the time of flare, a relationship between baseline MBDA value and flare risk was established. This may suggest that baseline MBDA score is only predictive of flares which are driven directly by inflammation. Interestingly, when each component of the MBDA score was analysed individually, only 3 of the 12 components (serum amyloid A (SAA), leptin and high sensitivity CRP) predicted flare. Studies suggests a close correlation between leptin levels and RA disease duration, activity and severity (Abella et al., 2017). The rapid production of SAA and its exceptionally wide dynamic range has proved advantageous as a biomarker of disease activity, with superiority over CRP in early RA studies (Hwang et al., 2016).

Ultrasound parameters, including power Doppler signal, had no predictive value in this study. This is likely a reflection of the high proportion of patients in this cohort who had ultrasound activity at baseline. In the POET study only 63% of patients had US sign of arthritis with positive power Doppler signal (Lamers-Karnebeek et al., 2017). This is partly explained by the cohort, which included a greater proportion of patients, one third, with low disease activity state (LDAS) above the DAS-28 remission cut-off. A large number of patients were on DMARD monotherapy, and only three were prescribed oral corticosteroids, which may explain the difference in power Doppler compared to other cohorts which have achieved LDAS with combination DMARDs and corticosteroid therapy. Scoring of PD was also more

stringent in this cohort compared to others (Saleem et al., 2012) leading to a much higher proportion of patients with PD signal being reported. The major limitation of ultrasound is that it remains a user-dependent technique. It is increasingly sensitive at demonstrating evidence of incomplete suppression of inflammation. The joints of healthy volunteers has been shown to display power Doppler signal (Ellegaard et al., 2007, Terslev et al., 2004) and treatment escalation studies have argued against very stringent ultrasound targets (Dale et al., 2016). Others have also shown that low grade PD signal and synovial hypertrophy may not necessarily reflect the presence of active synovitis in RA joints (Gartner et al., 2013). In this cohort, a high proportion had power Doppler activity at baseline and did not go on to flare. It may be postulated that a binary power Doppler cut-off might be insensitive in discriminating patients who are likely to flare.

This study also found that patients who flare were more likely to have erosive progression, worse quality of life and higher disease activity over 1 year. These findings consistent with previous studies (Ometto et al., 2016, Markusse et al., 2015a, Saleem et al., 2012) and emphasize the importance of flare and its relationship with patient outcomes. What remains unclear is whether flares are causally implicated in clinical outcome or if they are merely a biomarker of persistent low-grade disease. A flare may imply persistent uncontrolled inflammation contributing to disease progression, or a transient episode of inflammation (e.g. a 6 weeks flare within a stable 6-month period) that is sufficient to impact on long term outcome, or signify negative patient experience, a lack of self-control and unpredictability of the disease, which undoubtedly have psychological health implications.

There were several strengths of this study. The cohort was selected from routine care which is far more representative than a highly selective clinical trial population. Using patients in LDAS rather than remission enables access to a broader range of patients and is more in keeping with routine clinical

care. Furthermore, this was a deeply phenotyped cohort with extensive clinical and laboratory data at multiple time points across the study period.

There are potential limitations to this study. I must acknowledge the limitation of the REMIRA study sample size and the limited number of predictors identified could reflect a type two error. I also acknowledge issues with missing data, particularly with incomplete available ultrasound reports. However, I believe that the pattern of missing data met the assumptions of missing at random and I was able to successfully construct an imputation model to address this. I only registered flares during a visit to a rheumatologist and the actual flare rate might be higher. Potential flares in-between visits could have been detected by a flare questionnaire (Bykerk et al., 2014b) or alternative tools that permit remote monitoring. However, I would have only missed short lived flares (< 3 months), and these are of less clinical importance since they are less likely to lead to worse clinical outcomes (e.g. no radiographic progression) (van Herwaarden et al., 2015). REMIRA was an observational study and any modifications in medications were carried out according to the physicians and patients choices. Since treatment was not protocolised, this may have impacted on the rate of flares. A single failure model was used to identify predictors of flare, and thus changes in therapy after a flare event should not influence the analysis. It is however possible that treatment modifications, for example glucocorticoids during a flare may improve disease outcome at 12 months.

In conclusion, I have demonstrated that flares are common in RA patients with low disease activity states and are strongly associated with poor clinical outcomes. Therefore, preventing flares is clinically relevant yet relatively challenging. HAQ-DI, a measure of functional activity, was an important predictor of flare. However flares are complex events and not simply a reflection of inflammatory disease activity. It is possible that two distinct subtypes of flare might exist; an 'inflammatory' flare predominately driven by an increase in swollen joint count and ESR and a 'non-inflammatory' flare with a disproportionately

elevated tender joint count and a high patient global assessment score. Differentiating these two flare types may identify potential predictors. Further research is needed to explore if distinct flares exist and to categorize the potential predictors of each.

Chapter 4. Predictors of flare when tapering treatment; interrogation of the OPTTIRA cohort

This chapter comprises work defining predictors of flare in RA patients with LDA or clinical remission who are undergoing treatment tapering. Although tapering or discontinuation of TNFi therapy may be safe and effective for some patients, a proportion will flare during the process. Functional disability was predictive of flare in the REMIRA analyses of patients on stable therapy and possibly has a similar impact in a tapering cohort. Furthermore, depression is highly prevalent in RA and has the potential to impact flare incidence. In the OPTTIRA cohort, over one third of patients experienced at flare during the 12-month study period. A higher DAS28 score at study entry was associated with flare. Disability, fatigue and mental health also predicted flare, with only mental health remaining a statistically significant independent predictor. Given these findings, mental health and functional status should be considered in TNFi tapering decisions in order to optimise the likelihood of success.

4.1 Introduction

Disease activity-guided dose tapering or discontinuation of TNFi therapy appears to be feasible, safe and effective in a selected proportion of RA patients (van Herwaarden et al., 2015). However beyond the demonstration of clinical remission by the DAS28 score, there are no standardised methods to identify patients in whom treatment tapering is likely to be successful (Schett et al., 2016). Approximately 1/3rd to 2/3rd of patients flare when tapering or stopping TNFi treatment (Kuijper et al., 2015). There is growing evidence that even short term flare episodes contribute to worsening joint damage (Welsing et al., 2004) and poorer functional outcome (Markusse et al., 2015b). The ability to

accurately predict who may flare is likely to constitute a major improvement over the current trial-and-error tapering. At present, there are no consistently identified predictive markers for successful dose reduction (Tweehuysen et al., 2017).

Mental health constitutes a plausible marker for disease flare since poor mental health may influence symptom reporting and interfere with self-management behaviours. Mental health disorder is common in RA with major depression present in 17% of patients, and clinically significant depressive symptoms are found in up to 50% (Matcham et al., 2013). Worse mental health is associated with increased pain and fatigue (Kojima et al., 2009) and higher disease activity due to its influence on the TJC and the PGA components of the DAS28 score (Matcham et al., 2016b).

Worse mental health is negatively associated with remission in patients on TNFi therapy (Michelsen et al., 2017b, Matcham F, 2018). For those with stable disease, mental health has been identified as independent factor for flare. (Yilmaz et al., 2017). In addition to mental health, concurrent fibromyalgia (Ometto et al., 2016) and poorer physical quality of life measures (Saleem et al., 2012) have been shown to be associated with an increased risk of flare in patients with LDA on stable TNFi therapy, although it is less clear whether these measures are a reflection of worse mental health and inflammation.

To date, there are no studies directly addressing the role of mental health (depression, anxiety or low mood), fatigue and functional states in predicting flares in patients tapering their biological therapy. The aim of this study was to assess if baseline mental health and functional states measured by self-report screening questionnaires predict flare in RA patients with LDA who undergo treatment tapering of their TNFi agent as part of the Optimizing TNF Tapering in RA (OPTTIRA) trial.

4.2 Method

Study design and patients:

This study is a post-hoc analysis of the OPTTIRA trial. OPTTIRA was a multi-centre, prospective, randomized, open label study investigating TNFi tapering in established RA patients who are in sustained LDA (Ibrahim et al., 2017). The OPTTIRA trial consists of two phases: the randomised, controlled, open label, proof of principle phase (0-6 months), followed by the open exploratory phase (6-12 months) for patients who completed the initial trial period. All patients were receiving TNFi agents. They had met existing NICE criteria for starting these agents and had achieved a sustained good response, defined as DAS28 scores of 3.2 or less without an increase of more than 0.6, during the previous 3-month period. Patients were taking either Etanercept or Adalimumab at standard doses (50mg/week and 40mg/fortnight, respectively) and at least one concomitant csDMARD.

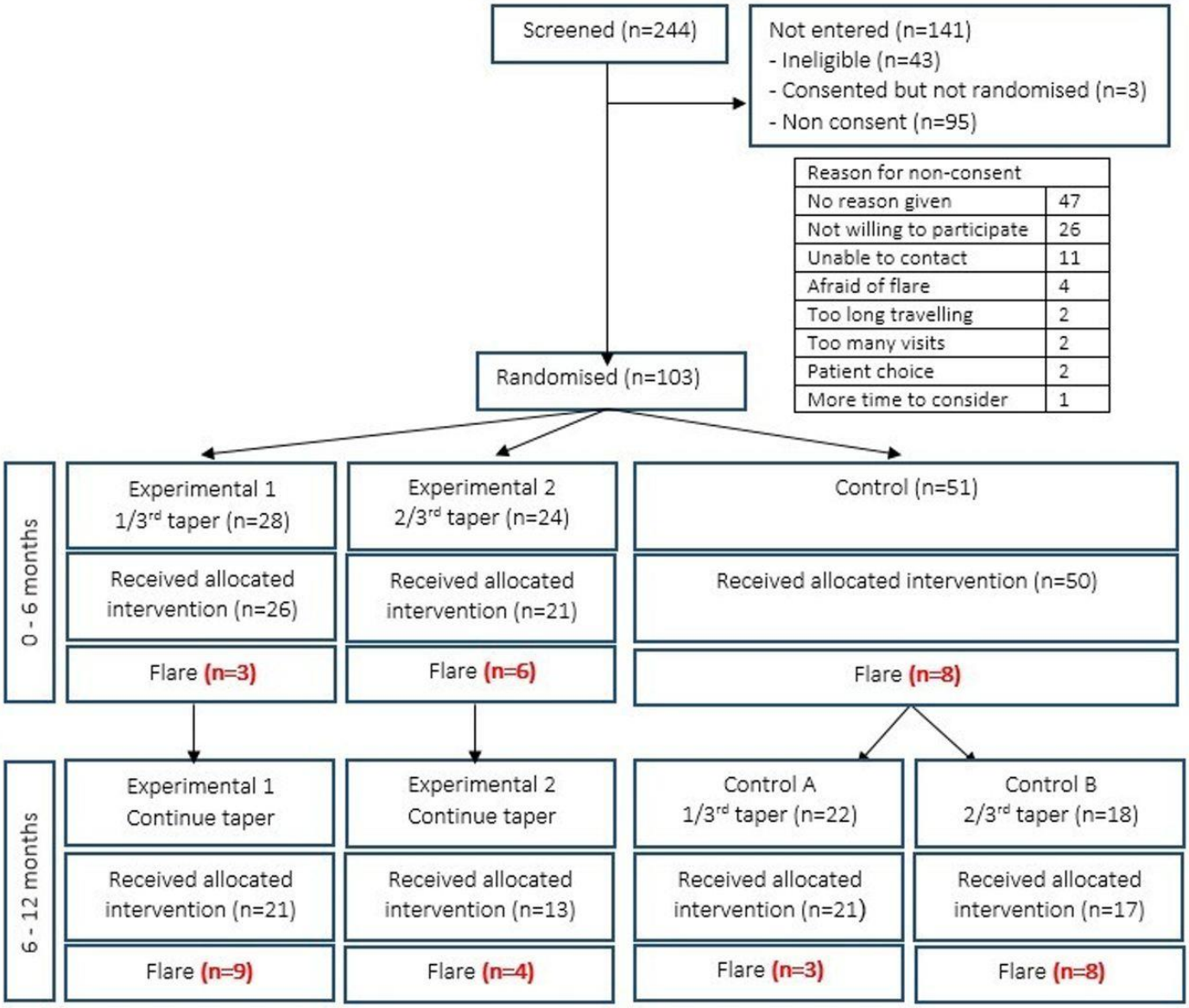
In the proof of principle phase of the study (0 months to 6 months), 50 patients were randomised to a control group (constant TNFi dose), and 47 patients to one of two experimental groups – *group 1* (26 patients) tapered TNFi by 33% whilst *group 2* (21 patients), tapered TNFi by 66%. At 6 months, patients who had not flared during the initial phase of the study, entered a second phase (6 months to 12 months). Those in experimental groups 1 and 2 continued tapering TNFi therapy to complete cessation, whilst patients from the control group were randomised into *control group A* (21 patients) who tapered TNFi by 33% or *control group B* (17 patients) who tapered by 66% (Figure 17). This post hoc analysis includes the entire cohort. The study was approved by the local ethics committee and was conducted according to the guidelines of the Declaration of Helsinki (REC Ref:10/H0720/69). Written informed consent was obtained from all patients.

Clinical assessments:

Baseline variables including patient demographics, RA disease duration and concomitant csDMARDs were collected prior to TNFi tapering. Disease-related and patient reported outcome measures that were assessed included the HAQ-DI, FACIT-F, EuroQol 5-dimension scale (EQ-5D) and the SF-36. Mental health was operationalised using the depression and anxiety question within the EQ-5D and the Mental Health (MH) subscale within the SF-36. The MH subscale shares similarities with generic depression screening questionnaires, such as the 9-item Patient Health Questionnaire (PHQ9) and has been demonstrated to perform reasonably well as a screening tool for depression in RA (Kingsley et al., 2011, Matcham et al., 2016c). A MH score cut-off of ≤56 was validated to detect depression in RA, with a sensitivity and specificity of 92.6% and 73.2% respectively (Matcham et al., 2016c).

The primary outcome was flare, defined as an increase in DAS28 scores ≥ 0.6 resulting in a DAS28 >3.2. The increase in DAS28 scores must include an increase in swollen joint count and be present on two occasions at least one week apart. An increase in DAS28 score ≥1.2 resulting in DAS28>3.2 between scheduled visits was also defined as flare irrespective of changes in the swollen joint count.

Figure 17. OPTTIRA trial consort flow chart



This consort flow chart illustrates the progress through screening and randomisation of patients in the OPTTIRA trial. It demonstrates the two phases: the randomised, controlled, open-label, proof-of-principle phase (0–6 months), followed by the open exploratory phase (6–12 months) for patients who completed the initial trial period, and the number of patients who flared at each stage.

Statistical analysis:

Descriptive statistics were provided with mean (+/− standard deviation (SD)), median (interquartile ranges (IQR)) or frequencies depending on data distribution. Discrete time survival regression models (complementary log-log link) were used to identify predictors of time to flare (Judith D. Singer, March 2003). Flare in the previous 3-month interval was the outcome variable and clinical and functional measurements the predictor variables. A multivariate discrete time survival model was applied adjusting for potential confounders: baseline age, gender, treatment arm, DAS28, and BMI. A *p* value <0.05 was regarded as being statistically significant. As this was an exploratory study no correction for multiple hypothesis testing was performed. A sensitivity analysis was also performed looking at the predictor variables at the assessment point immediately prior to the flare event. All analyses were performed with STATA 14.1 statistical software.

Missing data were addressed using a multiple imputation module. There were few baseline data missing (Table 8). At 3 and 6, month time points, there were less than 4% missing data, which were mainly psychological and functional measures, and around 10% missing data at 12 months. At 9 months, no psychological or functional measures were captured and there was 23% data missing on clinical variables. These data were considered missing at random. The imputation was 20 cycles, where at the end of the cycle one imputed dataset was created and the process was repeated to create 20 imputed datasets. The 20 datasets were combined using Rubin's rules therefore, the estimates and standard errors presented here are the combined ones.

Table 8. OPTTIRA cohort - missing data

Variable	Observations	Missing Variables
Baseline X-ray score	96	1
Tender joint count	448	37
Swollen joint count	449	36
ESR	447	38
VAS	446	39
DAS-28	447	38
CRP	449	36
Patient global assessment	448	37
PAIN score	446	39
HAQ-DI	371	114
EQ5D score	376	109
EQ5D Depression and anxiety question	435	50
FACIT-F	372	113
SF36-PCS	372	113
SF36-MCS	372	113
MH score	357	128

4.3 Results

Patient characteristics:

Between April 2011 and June 2013, 244 patients were screened, 103 were randomised and 97 accepted their allocated treatment (Figure 17). Baseline characteristics are given in Table 9. The majority of patients were on methotrexate in combination with their TNFi therapy (n=67, 69%) and the median disease duration was 11 years [IQR: 7-17]. Seventy-three patients (75%) fulfilled DAS28 remission criteria (DAS28 <2.6).

HAQ scores greater than 1, suggesting moderate to severe disability, were observed in 34% of patients. Median HAQ score was 0.5 [IQR: 0.13-1.38]. The median EQ-5D score was 0.76 [0.66-1.00] on a scale range from 1 to -0.594, where higher scores represent better quality of life. Twenty two percent of the cohort admitted to feeling symptoms of depression and anxiety on the EQ-5D depression question. Patients scored higher on the mental component of the SF-36 than the physical component [57 (49-60) versus 45 (34-52)], on a scale of 0–100 where higher scores represent better health states. The median SF-36 Mental Health (MH) subscale score was 84. A score of ≤56, the MH cut-off used to detect depression was observed in 11% of patients.

Characteristics of flare:

Forty-one patients (42%) flared over the 12-month period. In the first phase of the study (0 months to 6 months), 3 patients who tapered TNFi by 33% (experimental group 1) and 6 patients who tapered TNFi by 66% (experimental group 2) flared, whilst 8 patients in the control arm flared (figure 20). In the second phase of the study (6 months to 12 month), 9 patients in experimental group 1 and 4 patients

in experimental group 2, who were continuing tapering of TNFi therapy to complete cessation flared. In the control group, 3 patients who tapered TNFi by 33% (control group A) and 8 patients who tapered TNFi by 66% (control group B) flared.

There was a statistically significant difference in baseline SF36 MH and FACIT-F scores between patients who flared compared to those who did not; MH score [flare: 80 (68-88) versus no flare: 88 (72-92) p=0.04] and FACIT-F score [flare: 39 (31-44) versus no flare: 43 (37-46) p=0.03]. The lower the score the more severe the symptoms of depression or fatigue, respectively. There was a greater proportion of patients categorised with depression in the flare group by MH score ≤56 [8% versus 3%, p=0.03], but there was no difference when depression was categorised by the EQ5D anxiety and depression question [11% versus 10%, p=0.29]. There were no differences in baseline EQ5D or HAQ score between the two groups.

Table 9. OPTTIRA cohort - baseline demographics and clinical characteristics

Demographic variables	
Patients	97
Age, years*	57 (11)
Female gender	72 (74%)
Disease duration, years †	11.3 (7.3-16.7)
Smoking status - ex-smoker	32 (38%)
- current	12 (14%)
BMI	25.4 (22.6-29.4)
Clinical variables	
Treatment csDMARD - Methotrexate	67 (69%)
- Hydroxychloroquine	7 (7%)
- Sulfasalazine	4 (4%)
- Leflunomide	4 (4%)
- csDMARD combination	15 (15%)
Treatment bDMARD - Adalimumab	54 (56%)
- Etanercept	43 (44%)
Radiographic damage (Larsen score) †	51 (16-82)
Tender Joint counts (28 joints) †	0 (0-1)
Swollen joint counts (28 joints) †	0 (0-0)
Patient Global Assessment (mm) †	5 (1-16)
Erythrocyte Sedimentation Rate(mm/hr)†	8 (5-19)
C-Reactive Protein (mg/l)†	5 (2-6)
DAS28-ESR†	2.0 (1.25-2.57)
DAS28-ESR <2.6 (remission)	73 (75%)
Mental health variables	
Health Assessment Questionnaire score†	0.50 (0.13-1.38)
EQ-5D-3L score†	0.76 (0.66-1.00)
EQ-5D-3Ldepression question	21 (22%)
FACIT Fatigue Scale	41 (35-46)
SF-36 - Physical Component Summary *	45 (34-52)
- Mental Component Summary *	57 (49-60)
SF-36 MH score†	84 (72-92)
SF-36 MH (score < 56)	10 (10%)
Treatment arm	
Experimental 1 (taper 1/3rd)	26 (27%)
Experimental 2 (taper 2/3rd)	21 (22%)
Control A (taper 1/3rd)	27 (28%)
Control B (taper 2/3rd)	23 (24%)

Prediction of flare:

My primary analyses considered baseline patient characteristics in a flare prediction model (Table 10). A higher DAS-28 score at study entry was associated with increased hazard for flare. This association remained significant even after adjusting for co-variates [HR 1.96 (95% CI: 1.18, 3.24) p=0.04]. Disability (SF-36 physical component) predicted flare in the unadjusted model [HR per 10 units 0.74 (95% CI: 0.55, 0.99) p=0.05]. Fatigue (FACIT-F) and mental health (SF-36 MH) also predicted flare in univariate models [FACIT-F HR per 10 units 0.68 (95% CI: 0.47, 0.99) p=0.04] [MH HR per 10 units 0.81 (95% CI: 0.68, 0.96) p=0.01].

In adjusted analyses, only MH remained a statistically significant predictor of flare [HR per 10 units 0.74 (95% CI: 0.60, 0.93) p=0.01]. HAQ was not statistically significant predictor of flare, although the direction of association was consistent.

I also analysed the predictor variables at the assessment point immediately prior to the flare event. I used this time dependent analysis to determine whether flare is predicted by variables measures at closer time points to the event. There was no clinically meaningful difference in the point estimates of effects. The imputation model confirmed these findings (Table 11).

Table 10. OPTTIRA cohort - Cox proportional hazard estimates (95% CI) for flare

	Unadjusted hazard ratios	
	HR (95% CI)	*P value*
Demographic variables		
Age, years	1.02 (0.99-1.04)	0.24
Gender (male)	0.87 (0.42-1.82)	0.72
Disease duration, years	1.01 (0.97-1.04)	0.78
BMI	1.03 (0.97-1.09)	0.38
Treatment arm: Taper 1/3rd Taper 2/3rd	1.28 (0.55-2.98) 2.51 (1.06-5.96)	0.57 0.04
Clinical variables		
DAS28: - unadjusted - adjusted (age, gender, trial arm)	 1.86 (1.19, 2.92) 1.96 (1.18, 3.24)	 0.01 0.01
Mental health variables		
HAQ-DI: - unadjusted - adjusted (age, gender, trial arm) - adjusted (age, gender, trial arm, bmi, das28)	 1.45 (0.99, 2.13) 1.43 (0.91, 2.29) 1.16 (0.72, 1.87)	 0.06 0.13 0.53
EQ-5D: - unadjusted - adjusted (age, gender, trial arm) - adjusted (age, gender, trial arm, bmi, das28)	 0.28 (0.07, 1.24) 0.29 (0.06, 1.38) 0.51 (0.10, 2.58)	 0.09 0.12 0.42
EQ-5D depression anxiety: - unadjusted - adjusted (age, gender, trial arm) - adjusted (age, gender, trial arm, bmi, das28)	 1.42 (0.70, 2.87) 1.37 (0.64, 2.96) 1.51 (0.70, 3.28)	 0.33 0.41 0.29
FACIT: (per 10 unit) - unadjusted - adjusted (age, gender, trial arm) - adjusted (age, gender, trial arm, bmi, das28)	 0.68 (0.47, 0.99) 0.78 (0.48, 1.14) 0.77 (0.50, 1.16)	 0.04 0.18 0.20
SF-36 PCS: (per 10 unit) - unadjusted - adjusted (age, gender, trial arm) - adjusted (age, gender, trial arm, bmi, das28)	 0.74 (0.55, 0.99) 0.72 (0.52, 1.00) 0.86 (0.60, 1.23)	 0.05 0.05 0.41
SF-36 MCS: (per 10 unit) - unadjusted - adjusted (age, gender, trial arm) - adjusted (age, gender, trial arm, bmi, das28)	 0.90 (0.62, 1.31) 0.93 (0.60, 1.44) 0.83 (0.54, 1.28)	 0.58 0.74 0.41
SF-36 MH: (per 10 unit) - unadjusted - adjusted (age, gender, trial arm) - adjusted (age, gender, trial arm, bmi, das28)	 0.81 (0.67, 0.96) 0.80 (0.65, 0.98) 0.75 (0.60, 0.93)	 0.01 0.03 0.01

Table 11. OPTTIRA cohort - Cox proportional hazard estimates (95% CI) for flare in i) complete case analysis with baseline variable ii) complete case analysis with last observation prior to flare and iii) imputed analysis

	Complete case using baseline variables		Complete case using last observation		Imputed discrete time survival model	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years	1.02 (0.99-1.04)	0.24			1.02 (0.99-1.05)	0.24
Gender (male)	0.87 (0.42-1.82)	0.72			0.88 (0.43-1.82)	0.73
Disease dur, yrs	1.01 (0.97-1.04)	0.78			1.00 (0.97-1.04)	0.78
BMI	1.03 (0.97-1.09)	0.38			1.03 (0.97-1.09)	0.38
Treatment arm						
- Taper 1/3rd	1.28 (0.55-2.98)	0.57			1.29 (0.55-2.98)	0.57
- Taper 2/3rd	2.51 (1.06-5.96)	0.04			2.51 (1.06-5.96)	0.04
DAS28						
- unadjusted	1.86 (1.19, 2.92)	0.01	2.01 (1.45-2.78)	0.00	2.02 (1.45-2.80)	0.00
- adjusted (1)	1.96 (1.18, 3.24)	0.01	2.09 (1.51, 2.89)	0.00	2.11 (1.53, 2.92)	0.00
HAQ-DI						
- unadjusted	1.45 (0.99, 2.13)	0.06	1.52 (1.01-2.29)	0.04	1.51 (1.04-2.18)	0.03
- adjusted (1)	1.43 (0.91, 2.29)	0.13	1.46 (0.90-2.38)	0.12	1.48 (0.94-2.33)	0.09
- adjusted (2)	1.16 (0.72, 1.87)	0.53	1.14 (0.69-1.90)	0.61	1.13 (0.71-1.80)	0.61
EQ-5D						
- unadjusted	0.28 (0.07, 1.24)	0.09	0.22 (0.05-0.96)	0.04	0.21 (0.05-0.87)	0.03
- adjusted (1)	0.29 (0.06, 1.38)	0.12	0.27 (0.05-1.36)	0.11	0.23 (0.05-1.13)	0.07
- adjusted (2)	0.51 (0.10, 2.58)	0.42	0.53 (0.09-3.03)	0.48	0.50 (0.10-2.55)	0.40
EQ-5D depression						
- unadjusted	1.42 (0.70, 2.87)	0.33	1.74 (0.81-3.78)	0.16	1.96 (0.91-4.21)	0.09
- adjusted (1)	1.37 (0.64, 2.96)	0.41	1.66 (0.75-3.68)	0.21	1.85 (0.83-4.14)	0.13
- adjusted (2)	1.51 (0.70, 3.28)	0.29	1.63 (0.75-3.55)	0.22	1.76 (0.82-3.77)	0.15
FACIT *						
- unadjusted	0.68 (0.47, 0.99)	0.04	0.71 (0.49-1.03)	0.07	0.72 (0.51-1.03)	0.07
- adjusted (1)	0.78 (0.48, 1.14)	0.18	0.74 (0.50-1.11)	0.15	0.76 (0.52-1.10)	0.15
- adjusted (2)	0.77 (0.50, 1.16)	0.20	0.82 (0.56-1.19)	0.30	0.83 (0.58-1.18)	0.29
SF-36 PCS*						
- unadjusted	0.97 (0.94-1.00)	0.05	0.73 (0.53-1.00)	0.05	0.78 (0.58-1.07)	0.13
- adjusted (1)	0.97 (0.94-1.00)	0.05	0.73 (0.52-1.05)	0.09	0.79 (0.56-1.11)	0.17
- adjusted (2)	0.99 (0.95-1.02)	0.41	0.93 (0.60-1.42)	0.73	1.02 (0.69-1.51)	0.93
SF-36 MCS*						
- unadjusted	0.90 (0.62, 1.31)	0.58	0.75 (0.56-1.00)	0.05	0.74 (0.54-1.01)	0.06
- adjusted (1)	0.93 (0.60, 1.44)	0.74	0.75 (0.55-1.03)	0.08	0.75 (0.54-1.05)	0.09
- adjusted (2)	0.83 (0.54, 1.28)	0.41	0.77 (0.57-1.04)	0.09	0.75 (0.55-1.04)	0.08
SF-36 MH						
- unadjusted	0.81 (0.67, 0.96)	0.01	0.84 (0.69-1.03)	0.09	0.82 (0.68-0.99)	0.04
- adjusted (1)	0.80 (0.65, 0.98)	0.03	0.85 (0.68-1.05)	0.13	0.83 (0.67-1.01)	0.07
- adjusted (2)	0.75 (0.60, 0.93)	0.01	0.85 (0.68-1.05)	0.13	0.83 (0.67-1.02)	0.08

Adjusted 1 = adjusted for age, gender, trial arm.
Adjusted 2 = adjusted for age, gender, trial arm, bmi, das28

4.4 Discussion

To my knowledge, this is the first study to date to investigate the effect of mental health and functional states on the risk of flare when tapering TNFi therapy in RA patients. It was published in *Rheumatic and Musculoskeletal Disease (RMD Open)* in May 2018. Disability, fatigue and mental health as measured by patient-reported outcomes including SF-36 physical component, FACIT-F and the SF-36 mental health subscale (MH) predicted flare. Mental health as defined by the SF-36 MH was the only independent predictor of flare after adjusting for age, gender, treatment arm, DAS28, and BMI. The MH score ranges from 0 to 100, with lower scores indicating more severe depressive symptoms. With every 10-point decrease in MH score, the risk of flare increases by 19%. Both HAQ and EQ-5D were not statistically significant predictors of flare, although the direction of association was consistent.

Unlike the other variables, the SF-36 MH subscale specifically assesses depressive symptoms with items relating to low mood, nerves and restlessness. It shares similarities with generic depression screening tools, such as the 9-item Patient Health Questionnaire (Matcham et al., 2016c). In comparison, the other baseline measures assess quality of life and general mental health. For example, the SF-36 mental component summary is calculated by positively weighting the MH and 3 other psychological subscales (vitality, social function, emotional role). This suggests that depression alone can independently predict flare in patients who taper their TNFi agents. Depression can impact patient's perception and interpretation of their symptoms (Jensen et al., 2010) and is associated with poor health behaviour including reduced treatment adherence (DiMatteo et al., 2000). There is limited literature on the impact of depression in RA tapering cohorts. In patients who remain on stable treatment, depression has been shown to predict future disease activity, flare (Kekow et al., 2011, Yilmaz et al., 2017) and a poorer response to treatment (Matcham et al., 2016a, Hider et al., 2009). In drug tapering studies, HAQ

is the only patient-reported measures that has been evaluated, with lower scores associated with successful tapering in univariate analyses (Saleem et al., 2010, Takeuchi et al., 2015a).

The nocebo effect is a well-known phenomenon where patients' concerns and expectations about the value of a therapeutic intervention negatively influence adherence and treatment response. This has been considered in patients switching biologics from bio-originators to biosimilars, to explain a deterioration in therapeutic benefit, although the clinical features are complex and undefined (Pollard et al., 2010). It is acknowledged that patients with mental illness are more susceptible to the nocebo effect (Pollard et al., 2010) and it is plausible that this may also contribute to the association between unsuccessful drug tapering and flare in patients with poor mental health.

In this study, univariate analyses demonstrated that measures of quality of life status helped predict flare. However in the adjusted model, these measures did not remain statistically significant predictors. It is possible that measures of psychological and functional wellbeing correlate with other factors in a causal pathway; for example fatigue affects components of the DAS28 score, increasing the overall score and amplifying the risk of flare. Thus when adjusted for DAS28, the predictive value of these measures are lost. The direction of effect does not change in the adjusted model and it is likely that the loss in statistically significance is related to a loss of power due to the limited OPTTIRA sample size.

A higher DAS-28 score at entry was also predictive of flare in this study. The current literature on the predictive value of DAS-28 at point of TNFi tapering is conflicting. DAS28 was found to be a predictor of successful drug tapering in only half of the studies in which it was evaluated (Tweehuysen et al., 2017). In two TNFi discontinuation studies (remission induction by Remicade in RA (Tanaka et al., 2010) and the HONOR study (Tanaka et al., 2015)), analyses indicated a lower DAS28 cut-off value of 2.22 and 1.98 respectively, were required for successful drug tapering. The OPTIRA patient cohort was a LDA cohort,

in which a quarter of patient's baseline DAS28 scores were greater than the remission cut-off of 2.6. This may explain why DAS28 was shown to be a strong predictor of flare compared to exclusive remission cohorts.

When considering these findings, it is important to note the limited success in identifying biomarkers that predict dose tapering. Serological status (anti-CCP antibodies) (Haschka et al., 2016), ultrasound Doppler-detected synovitis (Haschka et al., 2016, Naredo et al., 2015), and the multi-biomarker disease activity score (Rech et al., 2015) have been individually evaluated. Although positive findings should be interpreted with caution due to reporting bias and multiple testing. A systematic review of all tapering studies identified adalimumab through level, the Sharp/van der Heijde erosion score and duration of symptoms at start of biologic to predict successful tapering (Tweehuysen et al., 2017).

The proportion of patient with depression in this population, defined by MH score ≤56 was relatively low. Clinical remission may be a significant influence of improvement in mental health states for patients both with and without baseline depression. It is recognised that patients who achieve clinical remission experience improvements in their depression and anxiety symptoms (Kekow et al., 2011). This may be due to reduction in pain and fatigue levels from control of RA disease activity, or it may be directly attributable to a reduction in pro-inflammatory cytokines including TNF-α, which can modulate neurotransmitter systems (Cavanagh et al., 2010). It is possible that consent bias resulted in the inclusion of "happier" patients, who are less likely to suffer from mental health disorder. Of the 244 patients screened, only 103 consented and entered randomisation (Figure 17). It has been reported that consenters are less likely to have a sensitive diagnosis such as a mood disorder (Jacobsen et al., 1999, Al-Shahi et al., 2005), and those who do are less likely to continue participation in clinical studies and can contribute to missing data.

Lastly, the OPTTIRA trial used a stringent definition of flare, which included the requirement for at least one swollen joint count to account for the increase in DAS28. In prior studies identifying an association between psychological measures and disease activity, the increase in DAS28 score has been driven primarily by tender joint count or global assessment score (Matcham et al., 2016a) which may be influenced by psychosocial factors (Pollard et al., 2010). In contrast, the captured flare events in the OPTTIRA study are more likely to represent a genuine inflammatory disease flare, and less likely influenced by low mood or depression. The OMERACT RA flare group recognise the limitation of DAS-28 in defining flare events. There is disparity between the classification of a flare by a patient, their physician and the DAS28 criteria. Agreement across these classifications is higher in patients in remission or LDA (Bykerk et al., 2016). A consensus-based core domain has been developed to provide a greater patient-centered tool to identify and measure flare in RA (Bykerk et al., 2014a). Improving the definition of flare may help identify and precisely quantify inflammatory flares which is vital in guiding successful drug tapering.

This study has several strengths. OPTTIRA was a pragmatically designed study, with less stringent inclusion and exclusion criteria and thus the cohort is far more representative than a highly selective clinical trial population. The inclusion of patients with low disease activity in addition to those in remission increases the generalisability of these findings. Lastly, this was a deeply phenotyped cohort with extensive clinical and laboratory data at multiple time points across the study period including precise date of flare events.

There are potential limitations to this study. Firstly, I must acknowledge the limitation of the OPTTIRA study sample size. The failure to detect other predictors of flare could reflect a type two error and the study's lack of power preclude robust conclusions. The high scores from the MH compared to population point-prevalence estimates may reflect that the sample size was not large enough to

capture sufficient patients with depression. Secondly, the study duration was relatively short and may not have provided a long enough period to allow patients to flare. I did not record or analyse sustained flares which may prove more important than potential transient flares. Lastly, there are a multitude of methods available to detect health-related quality-of-life and depression. The gold standard method for diagnosis of depression is psychiatric interview and diagnosis according to Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) criteria. Despite using both a disease-specific assessment (HAQ) and generic measures applicable to both the normal population and other disease groups (SF-36 and EQ5D), these are ultimately only screening tools. Estimates according to screening tools are based on predefined thresholds and tend to prioritize sensitivity over specificity which may result in overestimations of prevalence of depression (Matcham et al., 2013).

In conclusion, baseline depression, measured by SF-36 mental health scale and DAS-28 independently predict flare events in patients with sustained LDA who taper their TNFi agents. In addition to baseline depression, a range of psychological and functional states measured by patient-reported outcomes also predicted flare events in the OPTIRRA cohort although these were not be demonstrated to be independent risk factors. Based upon these findings, an assessment of mental health and functional status should be considered prior to dose reduction.

Chapter 5. Predictors of treatment non-response; the influence of increasing age

This chapter addresses the second aim of this thesis, identifying predictors of treatment non-response. The influence of increasing age on drug survival and treatment discontinuation in patients prescribed biological therapies was examined within the BSRBR-RA cohort. I hypothesised that older age may associate with a reduction in the immunogenicity of biologic therapies and thus the use of combination therapy with methotrexate might not prove as advantageous as it is in the younger cohort. This work identified that persistence with TNFi therapy was higher in younger patients. TNFi monotherapy compared to TNFi with concomitant methotrexate was associated with increased treatment failure. However when analysing the cohort by age, this finding only held true with younger patients. Older patients receiving TNFi monotherapy were less likely to discontinue therapy due to inefficacy and more likely to discontinue therapy from adverse events.

5.1 Introduction

In the management of RA, methotrexate continues to serve as the 'anchor drug', demonstrating efficacy as a first line therapy and is established as the standard of care worldwide (Pincus et al., 2003). Biologics are routinely used in patients who have failed treatment with methotrexate and/or other csDMARDs. Current national UK guidelines advocate administering biologics in combination with methotrexate therapy for those patients with an inadequate response to csDMARDs alone.

Randomized controlled trial data consistently demonstrate superior efficacy in controlling disease activity with TNF blockade in combination with methotrexate over TNFi monotherapy (Breedveld et al.,

2006, Klareskog et al., 2004, Emery et al., 2009, Keystone et al., 2009, Emery et al., 2015, Gomez-Reino, 2012). Longer-term observational data from national registries allow the examination of treatment continuation rates (drug survival). Drug survival is influenced by various factors including lack or loss of clinical efficacy, adverse events and poor adherence. Despite a good initial response to a TNF inhibitor, efficacy can wane over time. Secondary failure may result from the formation of antidrug antibodies (ADA) generated as a consequence of an immune response to the protein base agent, potentially neutralizing its therapeutic effect. Concomitant immunosuppression with methotrexate has a synergistic advantage. Methotrexate increases TNFi concentrations via the suppression of ADAs, prolonging TNFi drug survival (Kalden and Schulze-Koops, 2017). Registry data suggest superior drug survival with TNFi methotrexate combination compared to TNFi monotherapy (Soliman et al., 2011b, Zink et al., 2005, Jørgensen et al., 2015). A systematic review of published data from European and non-European registries reported that TNFi/csDMARD combinations reduced the risk of discontinuations from lack of efficacy (Souto et al., 2016). Individual registries also describe superior survival rates with TNFi/csDMARD combinations, driven by fewer terminations from adverse events (Kristensen et al., 2006).

Adults aged over 65 years old are under-represented in RA clinical trials and data mainly originate from post hoc analyses. Whilst the efficacy and safety of TNF blockade in patients over 65 years has been examined in observational studies, the results are conflicting (Radovits et al., 2009b, Hyrich et al., 2006b, Genevay et al., 2007, Filippini et al., 2010, Hetland et al., 2010, Krams et al., 2016, Radovits et al., 2009a). Some report reduced efficacy of TNFi in the elderly (Radovits et al., 2009a, Hetland et al., 2010) whilst other studies have not demonstrated an association with age and treatment response (Hyrich et al., 2006b, Filippini et al., 2010) or rates of TNFi discontinuation (Genevay et al., 2007). The reasons for TNFi discontinuation may differ depending on age, with older patients discontinuing more

frequently as a result of an adverse events and younger patients as a result of inefficacy (Filippini et al., 2010, Busquets et al., 2011).

Older age may associate with a reduction in the immunogenicity of biologic therapies. The aging immune system undergoes a gradual process of decline, termed immunosenescence. This affects both the innate and adaptive arms of the immune response. Key feature includes the suppression of phagocytosis by neutrophils and macrophages, altered cytokine production and a decrease in number and function of T and B lymphocytes and NK cells (Agarwal and Busse, 2010, Rink et al., 1998, Panda et al., 2009, Siegrist and Aspinall, 2009, Frasca et al., 2011, Boraschi et al., 2013). T cell diversity is maintained in patients up to 65 years of age, despite thymic output ceasing by approximately 50. After this, there is a rapid loss of clonal heterogeneity in individuals aged 75–80 years, with the T cell repertoire diversity a mere 1% that of a younger cohort (Pawelec, 2007). With increasing age there are important changes in antibody diversity with a decline in the ability to produce specific antibodies (Siegrist and Aspinall, 2009). It is plausible that the production of ADA which neutralize the effect of TNF inhibitors is less robust in elderly adults, reducing the risk of secondary failure and eliminating the need for concomitant immunosuppression

The primary objective of this study was to investigate drug survival rates with TNFi monotherapy compared to combination therapy with methotrexate in older adults. I hypothesise that TNFi drug survival is different in these patients and the use of combination therapy might not prove as advantageous in older adults as it is in the younger cohort.

5.2 Methods

Patient population:

Patients in this analysis were participants in the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA), a national prospective observational cohort study established in 2001 to monitor long-term safety of biological therapy. The BSRBR-RA methodology has been described previously (Watson et al., 2005). Ethical approval was granted in 2000 [MREC 00/8/053 (IRAS: 64202)]. Data uploaded to the BSRBR-RA by June 2016 were included in this analysis. All patients with RA, who were biologic naïve and commencing their first TNF inhibitors (infliximab, etanercept, adalimumab and certolizumab) were eligible for inclusion in the analysis. The initial BSRBR-RA biologic cohorts in 2001 were for etanercept and infliximab users. Adalimumab and certolizumab-pegol cohorts were recruited later. A golimumab cohort has not been recruited. I chose a cut-off in age at 75 years *a priori* for the primary analysis for pragmatic reasons. Previously analyses have used an age of 65, although this is probably too young to anticipate a difference attributable to immunosenescence. Due to diminishing sample sizes it would have been inappropriate to select a sample any higher than 75 years. My exploratory analyses have considered other age cut-off points.

Baseline data:

At registration baseline data included demographics, comorbidity, smoking status, RA disease duration, RA disease activity (DAS-28), Health Assessment Questionnaire (HAQ) and csDMARD and corticosteroid exposure. Comorbidities were obtained from the patient's medical records, using a pre-specified list of coexisting conditions. Comorbidity burden was scored using the Rheumatic Disease Comorbidity Index (RDCI), composed of 11 weighted past or present comorbid conditions. The RDCI performs well in

predicting RA specific outcomes including disability, medical costs, hospitalisation and death (Michaud and Wolfe, 2007, Wolfe, 2010, England et al., 2015).

Follow-up:

Follow-up data were collected every 6 months for the first 3 years by questionnaires sent to patients and their supervising rheumatology teams, and annually thereafter by questionnaires sent to the supervising rheumatology team only. Data on adverse events were captured from clinician questionnaires, from 6-monthly patient diaries detailing new hospital admissions, and by linkage to NHS Digital which provides mortality data. NHS Digital has near complete capture of mortality data in the UK as all deaths (irrespective of where the death occurs) are centrally registered.

Outcome:

The primary outcome was persistence with first TNFi therapy, which was defined as the duration of time the patients continued to receive TNF blockade. Individuals were considered 'at risk' from treatment start for 5 years, or until treatment stop date, date of the last follow-up or date of death, whichever came first. Temporary stops of less than 90 days, after which the patient restarted the same anti-TNF therapy were counted as continuous use of the drug. Secondary outcomes included reason for TNF discontinuation separated according to inefficacy and adverse events.

Statistical analysis:

The cohort was divided according to age at registration: <75 and ≥75 years. Baseline characteristics were tabulated and tested for statistically significant imbalance using Chi-square, Mann–Whitney or t-tests, as appropriate. Kaplan–Meier survival curves were used to describe the persistence with anti-

TNF therapy. The incidence rate of treatment discontinuation was calculated per 100 patient-years with 95% confidence interval. Cox proportional hazards models were used to compare the risk of TNFi discontinuation between patients prescribed TNFi monotherapy compared to those receiving TNFi methotrexate combination (the reference group). Three models were developed, evaluating treatment discontinuation; 1) any cause 2) inefficacy and 3) adverse events. For the separate inefficacy and adverse event analyses, a competing risk survival model was used following the Fine & Gray method allowing for accurate estimates of cumulative incidence (Fine and Gray, 1999). Multivariable adjustment was made for the following baseline covariates: age, sex, disease duration, DAS28, HAQ, RDCI, smoking status and steroid exposure.

Baseline missing data were addressed using multiple imputation, with multivariate sequential imputation using chained equations for 20 imputations. The predictor and outcome data were near complete; only 1 patient did not have a recorded age. There were missing data for several baseline variables used in the multivariate analysis. Data on gender, comorbidity and steroid use were complete. Missing data are presented below (Table 12). All missing data were imputed regardless of the reason or reasons it was missing. The following variables with complete data were utilised for the imputation: age; gender; comorbidity; steroid use; previous DMARDs exposure, current DMARDs therapy, choice of TNF therapy, time to TNF therapy discontinuation and reason for discontinuation. Linear and logistic regression were performed to impute the normally distributed and dichotomous variables respectively. The HAQ-DI was analysed as a continuous variable. I did not have access to item level data for the HAQ-DI to Rasch transform it. I used predictive mean matching approach in the imputation model to account for this. The data were imputed using multivariate sequential imputation using chained equations. Firstly, all missing values were filled in by simple random sampling with replacement from the observed values. The first variable with missing values was regressed on all other variables. The imputation was 20 cycles, where at the end of the cycle one imputed dataset was created and the process was repeated

to create 20 imputed datasets. The 20 datasets were combined using Rubin's rules, therefore the estimates and standard errors presented here are the combined ones.

To address confounding by indication, a sensitivity analysis was performed using a propensity score (PS) model employing inverse probability of treatment weights for patients receiving TNFi monotherapy compared to those receiving TNFi-methotrexate combination. A single-variable logistic regression model was used to identify baseline covariates that predicted treatment choice (monotherapy versus methotrexate combination therapy). A multivariable logistic regression model using significant predictors was used to create a single propensity score for each individual. A Hosmer-Lemeshow test was used to assess the regression equation. A propensity score model was created including the following covariates: age, gender, disease duration, RDCI, DAS28, HAQ, smoking status and steroid exposure. The inverse of the probability (or the inverse of 1 minus the probability in the monotherapy cohort) was then used as the treatment weight in the analysis. Truncation of weights was used to prevent a small number of larger weights de-stabilising the model. The balancing of the cohorts using the weighted model was tested by comparing standardised differences between cohorts. The weighted means and standard differences are shown in Table 13. Further analyses compared TNFi discontinuation in patients prescribed TNFi with other csDMARDs combinations. All analyses were undertaken using Stata 15 (StataCorp., College Station, TX, USA).

Table 12. BSRBR-RA cohort - missing data

Variable	Observations	Missing Variables
Age	15699	1
Disease duration	15,537	163
DAS28-ESR	14,997	703
HAQ-DI	12,659	3041
Smoking status	12,986	2741
Seropositive	15,140	560

Table 13. BSRBR-RA cohort - comparison of baseline covariates in weighted cohorts with propensity score

	Mean in TNF Monotherapy	Mean in TNF-MTX combination	Standardised difference
Before weighting			
Baseline Age (years)	57.82	54.88	0.236
Female	0.76	0.75	0.025
RDCI Score	1.15	0.98	0.149
Disease Duration in years	14.93	13.40	0.156
Baseline DAS28 Score	6.61	6.49	0.118
Baseline HAQ Score	2.111	1.99	0.209
Steroid users	0.51	0.40	0.231
Smoker	0.63	0.61	0.044
After weighting – unimputed baseline data			
Baseline Age (years)	55.82	55.95	-0.010
Female	0.75	0.76	-0.008
RDCI Score	1.04	1.04	-0.002
Disease Duration in years	13.99	13.99	0.000
Baseline DAS28 Score	6.52	6.53	-0.011
Baseline HAQ Score	2.03	2.04	-0.008
Steroid users	0.44	0.44	-0.005
Smoker	0.62	0.62	-0.003
After weighting - imputed baseline data			
Baseline Age (years)	56.41	55.75	0.048
Female	0.77	0.75	0.060
RDCI Score	1.05	1.05	0.002
Disease Duration in years	14.16	13.93	0.023
Baseline DAS28 Score	6.55	6.52	0.034
Baseline HAQ Score	2.06	2.03	0.020
Steroid users	0.46	0.43	0.003
Smoker	0.62	0.62	-0.052

5.3 Results

Patient characteristics:

Of 23,411 subjects registered in the BSRBR-RA, 15,700 were biologic naïve and commencing their first TNF inhibitor. Ninety five percent of the cohort were younger than 75 years old. Overall mean age was 55 (SD 12·9), with a median disease duration of 10 years (IQR 5-18). Baseline mean DAS-28 was 6·42 (SD 1·06), reflective of a UK biologic initiation cohort. Baseline characteristics are in Table 14.

Patients 75 years and older:

As expected, the ≥75 cohort demonstrated greater comorbidity burden compared to the younger cohort (RDCI score ≥1 in 72% versus 56%, p <0·001), with a higher prevalence of both cardiac and respiratory disease. RA disease activity measured by DAS28-ESR was higher in the ≥75 cohort (mean DAS28 6·52 versus 6.42, p=0·009). This was driven by a higher ESR (median 43 (IQR 26-68) versus 38 (21-61), p<0·0001) with no significant difference in the number of tender and swollen joints or global VAS between the two age groups. A greater proportion of the ≥75 cohort were prescribed prednisolone (52% versus 39%, p <0·001), however there was no difference in the number of previous csDMARDs or choice of TNFi agents. Older patients were more likely to be prescribed TNFi monotherapy over combination with csDMARDs (35% versus 24%, p<0·0001).

Treatment regimens:

Seventy five percent of patients were prescribed TNFi in combination with csDMARDs, rather than as monotherapy. There were several key differences comparing patients on TNFi monotherapy to combination therapy; patients on TNFi monotherapy demonstrated greater comorbidity burden,

elevated markers of RA disease activity and disability, and a higher number of previous failed csDMARDs and concurrent prednisolone exposure (Table 15).

Table 14. BSRBR-RA cohort- baseline characteristics by age group (<75 years old & ≥75 years old)

	<75 years old	≥75 years old	Stat. imbalance
Total cohort, n (%)	14, 932 (95.1)	768 (4.9)	
Age, yrs.,	55 (46-63)	77 (76-80)	
Female sex, n (%)	10,788 (72.3)	627 (81.6)	<0.001†
Smoking status, n (%)			
- Current	2,648 (22.3)	43 (7.0)	<0.001†
- Ever	7,597 (61.6)	393 (60.3)	0.53†
Comorbidity (RDCI score ≥1), n (%)	8,303 (55.6)	551 (71.7)	<0.001†
- Cardiac (MI, stroke, angina)	968 (6.5)	133 (17.3)	<0.001†
- Respiratory (asthma, COPD)	2,080 (13.9)	129 (16.9)	<0.03†
Seropositive (RF), n (%)	8,437 (58.7)	485 (64.3)	<0.002†
Disease duration, yrs.	10 (5-18)	14 (7-23)	<0.0001*
Number of previous csDMARDs	3 (2-5)	3 (2-5)	0.33*
TNFi, n (%)			
- Infliximab	3955 (26.5)	209 (27.2)	
- Etanercept	5374 (36.0)	265 (34.5)	0.82†
- Adalimumab	4744 (31.8)	246 (32.0)	
- Certolizumab	859 (5.8)	48 (6.3)	
TNFi Monotherapy, n (%)	3642 (24.4)	268 (34.9)	<0.001†
TNFi/csDMARDs Combination			
- Methotrexate	5776 (38.7)	252 (33.8)	
- Sulfasalazine	430 (2.9)	21 (2.7)	
- Leflunomide	667 (4.5)	43 (5.6)	
- Two csDMARDs	2930 (19.6)	111 (14.5)	
- Three csDMARDs	781 (5.2)	30 (3.9)	
- Other combination	706 (4.7)	43 (5.6)	
Prednisolone, n (%)	5,867 (39.3)	401 (52.2)	<0.001†
DAS28-ESR, mean (SD)	6.42 (1.1)	6.52 (1.0)	0.01*
SJC28, mean (SD)	10.7 (6.2)	10.6 (6.0)	0.84*
TJC28, mean (SD)	15.2 (7.5)	15.1 (7.9)	0.67*
Global VAS	75 (62-87)	75 (60-87)	0.20*
ESR	38 (21-61)	43 (26-68)	<0.0001*
CRP mg/l	26 (11-56)	29 (13-60)	0.12*
HAQ, median (IQR)	2.125 (1.625-2.375)	2.25 (2-2.625)	<0.0001

Values are gives as median (IQR), unless otherwise specified by n (%) or mean (SD). Statistical imbalance tested χ^{2} † or kwallis*

Table 15. BSRBR-RA cohort - baseline table comparing patients on combination csDMARD and TNFi versus patients prescribed TNFi monotherapy

	Combination therapy	Monotherapy	Stat. imbalance
Total cohort, n (%)	11, 790 (75.1)	3910 (24.9)	
Age, yrs., mean (SD)	55 (46-64)	58 (48-66)	<0.0001*
Female sex, n (%)	8605 (73.0)	2810 (71.9)	0.17
Smoking status, n (%)			
- Current	1997 (21.5)	694 (21.8)	0.65†
- Ever	5917 (61.0)	2073 (63.0)	0.05†
Comorbidity (RDCI score ≥1)	6467 (54.9)	2387 (61.1)	<0.001†
- Cardiac (MI, stroke, angina)	764 (6.5)	337 (8.6)	<0.001†
- Respiratory (asthma, COPD)	1615 (13.7)	594 (15.2)	<0.02†
Seropositive (RF), n (%)	6794 (59.2)	2128 (58.2)	<0.29†
Disease duration, yrs.	10 (5-17)	12 (6-21)	<0.0001*
Number of previous DMARDs	3 (2-4)	4 (3-5)	<0.0001*
TNF, n (%)			
- Infliximab	3882 (32.9)	282 (7.2)	
- Etanercept	3349 (28.4)	2290 (58.6)	<0.001†
- Adalimumab	3791 (32.2)	1199 (30.7)	
- Certolizumab	768 (6.5)	139 (3.6)	
Prednisolone, n (%)	4449 (37.7)	1819 (46.5)	<0.001†
DAS28-ESR, mean (SD)	6.39 (1.0)	6.54 (1.1)	<0.001*
SJC28, mean (SD)	10.7 (6.1)	10.8 (6.3)	0.36*
TJC28, mean (SD)	15.1 (7.4)	15.5 (7.8)	0.03*
Global VAS	75 (60-85)	78 (64-90)	<0.0001*
ESR	36 (21-60)	42 (25-67)	<0.0001*
CRP mg/l	25 (11-53)	29 (12-65)	<0.0001*
HAQ-DI, median (IQR)	2 (1.625, 2.375)	2.25 (1.75, 2.5)	<0.0001*

Values are gives as median (IQR), unless otherwise specified by n (%) or mean (SD). Statistical imbalance tested χ^{2} † or kwallis*

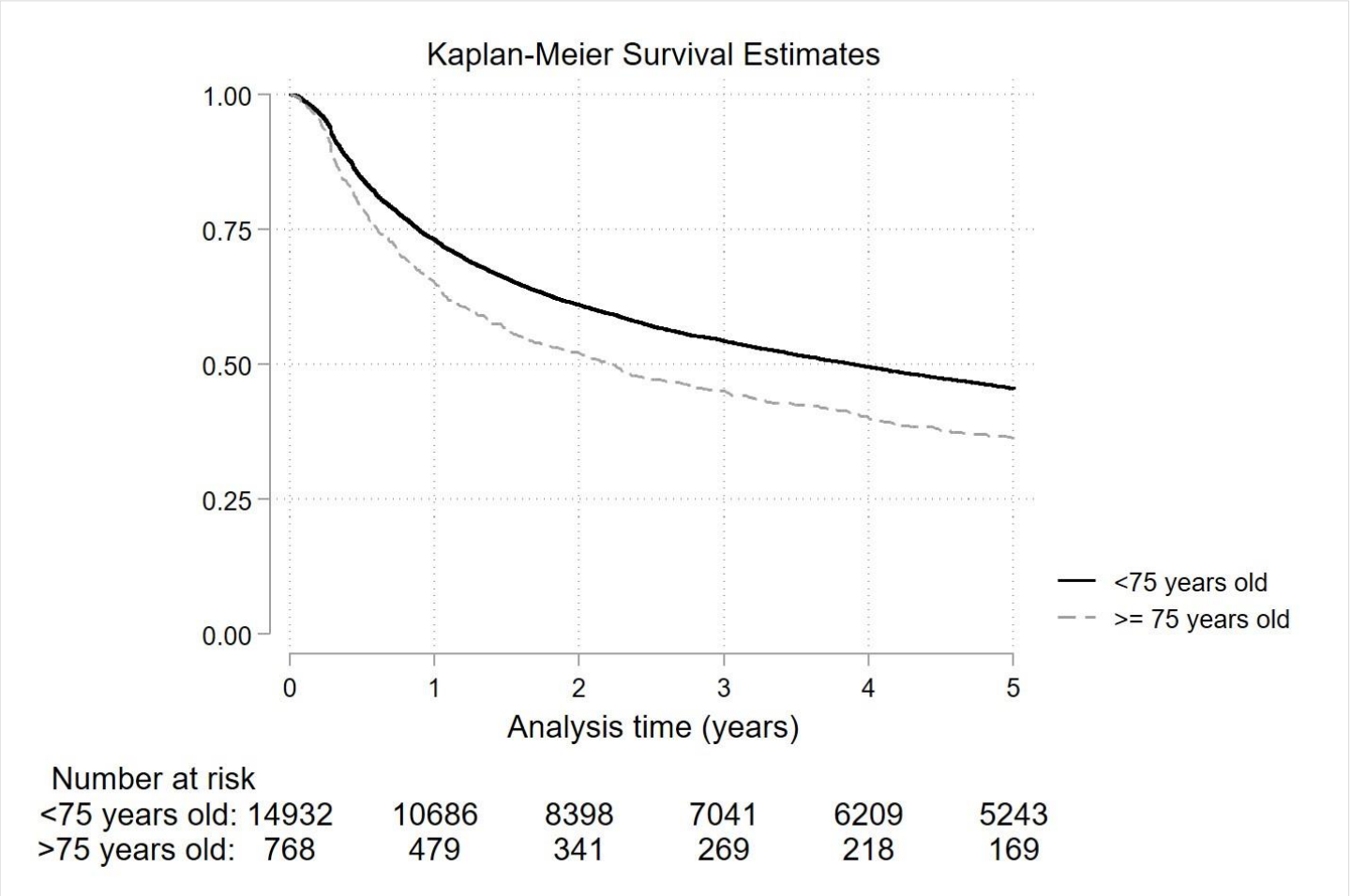
Persistence of TNF blockade:

Fifty two percent of the cohort (n=8,206) discontinued their first TNFi therapy during the follow up period. With 44,642 persons years follow up, the overall incidence of discontinuation was 18·4 (95% CI 18·0-18·8) per 100 patient years. Major reasons for discontinuation were adverse event (40%) and inefficacy (41%).

Persistence with TNFi therapy was higher in the younger cohort (Figure 18 and Table 16). The crude incidence rates per 100 patient years for TNFi discontinuation were higher in the ≥75 compared to <75 age group; all cause: incidence rate (IR) 25.5 (95% CI 23·2 to 27·9) versus IR 18.1 (95% CI 17·7 to 18·5), inefficacy: IR 8·4 (95% CI 7·2 to 9·9) versus IR 7·4 (95% CI 7·2 to 7·7) and adverse events: IR 11.8 (95% CI 10.3 to 13.6) versus IR 7·1 (95% CI 6·9 to 7·4) (Table 16).

Overall, patients receiving TNFi monotherapy were more likely to discontinue TNF blockade compared to patients receiving TNFi/methotrexate combination therapy [hazard rate (HR) 1·12 (95% CI 1·06 to 1·18) p<0·001]. This finding was maintained when restricting the analysis to the younger cohort but not the older cohort, with no statistically significant difference in the hazard rate for discontinuation between TNFi monotherapy and TNFi methotrexate combination (Figure 19 and Table 16)

Figure 18. BSRBR-RA cohort - Kaplan–Meier estimates of crude persistence with TNFi therapy by age



This Kaplan Meier graph demonstrates TNFi survival estimates over the 5-year period for patients in both age cohorts. The risk table below illustrates the number of patients continuing TNFi therapy at each year time point.

Table 16. BSRBR-RA cohort - incidence rate and Cox proportional hazard estimates (95% CI) for TNFi discontinuation by age group (<75 years old & ≥75 years old)

	<75yrs (n=14932)	≥75yrs (n=768)	Total
Number of subjects	14932	768	15700
Patients with TNFi failure, n (% of cohort)	7756 (51.9)	450 (58.6)	8206 (52.3)
Reason for TNFi failure, n (%)			
- Inefficacy	3193 (41.2)	149 (33.1)	3342 (40.7)
- Adverse effect	3044 (39.3)	209 (46.4)	3253 (39.6)
- Remission	51 (0.07)	5 (1.1)	56 (0.7)
- Other	1171 (15.1)	75 (16.7)	1246 (15.2)
- Missing	297 (3.8)	12 (2.7)	309 (3.8)
TNFi failure – all cause			
Follow up (Person-years)	42876	1766	44642
No. of TNFi patients with TNFi failures	7756	450	8206
Incidence rate / 100 patient years (95% CI)	18.1 (17.7-18.5)	25.5 (23.2-27.9)	18.4 (18.0-18.8)
Hazard ratio (95% CI) (ref methotrexate)			
- Unadjusted; Monotherapy	1.11 (1.05-1.17) *	1.13 (0.90-1.41)	1.12 (1.06-1.18) *
- Adjusted (imputed); Monotherapy	1.07 (1.01-1.13) †	1.15 (0.91-1.45)	1.08 (1.02-1.14) †
- Propensity (imputed); Monotherapy	1.06 (1.00-1.12)	1.12 (0.90-1.40)	1.06 (1.01-1.13) †
TNFi failure – inefficacy			
Follow up (Person-years)	42876	1766	44642
No. of TNFi patients with TNFi inefficacy	3193	149	3342
Incidence rate / 100 patient years (95% CI)	7.4 (7.2-7.7)	8.4 (7.2-9.9)	7.5 (7.2-7.7)
Hazard ratio (95% CI) (ref methotrexate)			
- Unadjusted; Monotherapy	1.06 (0.97-1.16)	0.66 (0.43-0.99) †	1.03 (0.95-1.13)
- Adjusted (imputed); Monotherapy	1.06 (0.97-1.16)	0.63 (0.41-0.97) †	1.03 (0.94-1.13)
- Propensity (imputed); Monotherapy	1.06 (0.97-1.16)	0.69 (0.45-1.04)	1.04 (0.95-1.13)
TNFi failure – adverse events			
Follow up (Person-years)	42876	1766	44642
No. of TNFi patients with TNFi adverse events	3044	209	3253
Incidence rate / 100 patient years (95% CI)	7.1 (6.9-7.4)	11.8 (10.3-13.6)	7.3 (7.0-7.5)
Hazard ratio (95% CI) (ref methotrexate)			
- Unadjusted; Monotherapy	1.21 (1.11-1.32) *	1.41 (1.02-1.96) †	1.23 (1.13-1.34) *
- Adjusted (imputed); Monotherapy	1.13 (1.03-1.23) *	1.46 (1.05-2.03) †	1.14 (1.05-1.25) *
- Propensity (imputed); Monotherapy	1.11 (1.02-1.22) *	1.35 (0.97-1.88)	1.13 (1.04-1.23) *

*= p-value <0.01. † = p-value <0.05. Reference group = TNFi-Methotrexate combination. Adjusted for age, gender, disease duration, Rheumatic Disease Comorbidity Index, smoking, DAS28, HAQ-DI and steroid use

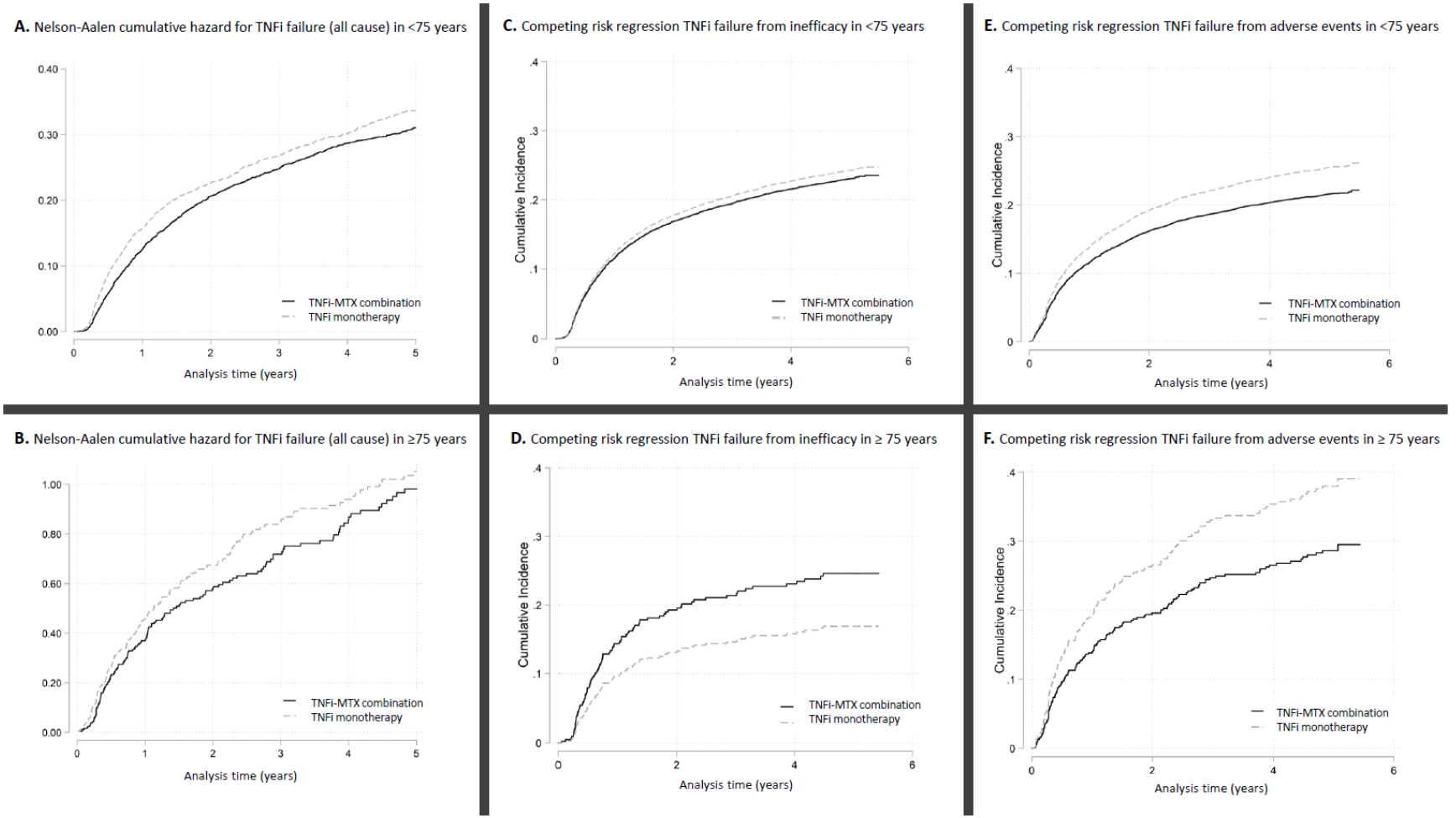
When examining TNFi discontinuation by cause, patients in the ≥75 cohort receiving TNFi monotherapy were 34% less likely to discontinue TNFi due to inefficacy compared to patients receiving TNFi methotrexate combination [HR 0·66 (0.43 to 0·99) p=0·04]. This finding was not seen in the younger cohort. Patients <75 years old receiving TNFi monotherapy were 6% more likely to discontinue TNFi due to inefficacy compared to patients receiving TNFi methotrexate, although this was not statistically significant. When examining TNFi discontinuation due to adverse events, patients in both age groups were more likely to discontinue therapy when prescribed TNFi monotherapy compared to TNFi methotrexate combination [≥75 HR 1·41 (1·02 to 1·96) p=0·04] and <75 HR 1·21 (1·11 to 1·32) p<0·001] (Figure 19 and Table 16).

All results remained statistically significant in the multivariable analyses, with no meaningful difference in point estimates from complete case analysis and those obtained using the imputed data (Table 18). The propensity score model also had minimal influence on the point estimates, but the confidence included 1, indicating there may not sufficient evidence to conclude the observed difference is reliable in the over 75's (Table 17).

Analyses investigating other TNFi/csDMARD combinations identified a greater risk of discontinuing TNF blockade in the <75 cohort if co-prescribed leflunomide compared to methotrexate [all cause: adjHR 1·22 (1·08 to 1.38) p=0·001, and adverse event: adjHR 1·36 (1·13 to 1·63) p=0·001]. Patients in this younger cohort were also less likely to discontinue anti-TNF if co-prescribed two csDMARDs compared with methotrexate alone [all cause: adjHR 0·85 (0·78 to 0·92) p<0·001, and adverse event: adjHR 0·83 (0·72 to 0·95) p=0·02] (Table 18). Exploratory analyses considered other age cut-off points (65 years

and 70 years). The reduced risk of TNFi discontinuation due to inefficacy in patients receiving monotherapy was no longer apparent at younger age cut off (Table 19).

Figure 19. BSRBR-RA cohort - cumulative hazard estimates of TNFi failure with TNFi monotherapy and TNFi-MTX combination therapy, by cause



These Nelson-Aalen graphs demonstrates the cumulative hazard of discontinuing TNF inhibition for any reason, and for inefficacy or adverse events, by age cohort in patients receiving TNFi monotherapy compared to those receiving TNF-MTX combination. Patients in the ≥75 cohort receiving TNFi monotherapy were less likely to discontinue TNFi due to inefficacy compared to patients receiving TNFi methotrexate combination. This finding was not seen in the younger cohort. Patients in both age cohorts receiving TNFi monotherapy were more likely to discontinue TNFi due to adverse events compared to patients receiving TNFi MTX combination

Table 17. BSRBR-RA cohort - Cox hazard estimates for TNFi discontinuation from complete case analysis, multiply imputed data and propensity model

	<75yrs	≥75yrs	Total
TNF failure – all cause (reference methotrexate)			
Complete case analysis			
- Unadjusted Monotherapy	1.11 (1.05-1.17) *	1.13 (0.90-1.41)	1.12 (1.06-1.18) *
- Adjusted; Monotherapy	1.08 (1.01-1.15) †	1.16 (0.89-1.52)	1.08 (1.01-1.15) *
Multiply imputed data			
- Adjusted; Monotherapy	1.07 (1.01-1.13) *	1.15 (0.91-1.45)	1.08 (1.02-1.14) *
Propensity score model			
- Complete case analysis	1.05 (0.98-1.13)	1.15 (0.89-1.49)	1.06 (0.99-1.13)
- Multiply imputed data	1.06 (1.00-1.12) †	1.12 (0.90-1.40)	1.06 (1.01-1.13) †
TNF failure – inefficacy (reference methotrexate)			
Complete case analysis			
- Unadjusted Monotherapy	1.06 (0.97-1.16)	0.66 (0.43-0.99) †	1.03 (0.95-1.13)
- Adjusted; Monotherapy	1.01 (0.91-1.12)	0.59 (0.35-0.97) †	0.99 (0.89-1.09)
Multiply imputed data			
- Adjusted; Monotherapy	1.06 (0.97-1.16)	0.63 (0.41-0.97) †	1.03 (0.94-1.13)
Propensity score model			
- Complete case analysis	1.01 (0.91-1.12)	0.65 (0.41-1.05)	0.99 (0.89-1.10)
- Multiply imputed data	1.06 (0.97-1.16)	0.69 (0.45-1.04)	1.04 (0.95-1.13)
TNF failure – adverse events (reference methotrexate)			
Complete case analysis			
- Unadjusted Monotherapy	1.21 (1.11-1.32) *	1.41 (1.02-1.96) †	1.23 (1.13-1.34) *
- Adjusted; Monotherapy	1.17 (1.05-1.30) *	1.63 (1.10-2.40) †	1.19 (1.08-1.31) *
Multiply imputed data			
- Adjusted; Monotherapy	1.13 (1.03-1.23) *	1.46 (1.05-2.03) †	1.14 (1.05-1.25) *
Propensity score model			
- Complete case analysis	1.14 (1.03-1.27) †	1.50 (1.03-2.20) †	1.16 (1.04-1.28) *
- Multiply imputed data	1.11 (1.02-1.22) *	1.35 (0.97-1.88)	1.13 (1.04-1.23) *

*= p-value <0.01. † = p-value <0.05. Reference group = TNFi-Methotrexate combination. Adjusted for age, gender, disease duration, Rheumatic Disease Comorbidity Index, smoking, DAS28, HAQ-DI and steroid use

Table 18. BSRBR-RA cohort - incidence and Cox hazard estimates for TNFi discontinuation by combination therapy

	<75yrs	≥75yrs	Total
TNF failure – all cause			
Follow up (Person-years)/100	42876	1766	44642
No. of TNF patients with TNF failures	7756	450	8206
Incidence / 100 patient years (95% CI)	18.1 (17.7-18.5)	25.5 (23.2-27.9)	18.4 (18.0-18.8)
Unadjusted HR (95% CI) – ref MTX			
- Monotherapy	1.11 (1.05-1.17) *	1.13 (0.90-1.41)	1.12 (1.06-1.18) *
- Sulfasalazine	0.95 (0.82-1.09)	1.48 (0.87-2.53)	0.97 (0.85-1.11)
- Leflunomide	1.23 (1.11-1.37) *	1.32 (0.88-1.98)	1.24 (1.12-1.38) *
- Two csDMARDs	0.82 (0.76-0.87) *	0.91 (0.66-1.24)	0.82 (0.77-0.88) *
- Three csDMARDs	0.90 (0.80-1.01)	1.04 (0.62-1.74)	0.90 (0.81-1.01)
Adjusted HR (95% CI) - – ref MTX			
- Monotherapy	1.08 (1.01-1.15) †	1.17 (0.90-1.53)	1.08 (1.01-1.15) *
- Sulfasalazine	1.01 (0.85-1.20)	1.85 (0.99-3.48)	1.04 (0.88-1.23)
- Leflunomide	1.22 (1.08-1.38) *	1.40 (0.89-2.18)	1.23 (1.10-1.39) *
- Two csDMARDs	0.86 (0.79-0.94) *	1.08 (0.74-1.57)	0.88 (0.81-0.95) *
- Three csDMARDs	0.96 (0.84-1.11)	0.93 (0.47-1.85)	0.97 (0.85-1.11)
TNF failure – inefficacy			
Follow up (Person-years)	42876	1766	44642
No. of TNF patients with TNF inefficacy	3193	149	3342
Incidence / 100 patient years (95% CI)	7.45 (7.19-7.71)	8.44 (7.18-9.91)	7.49 (7.24-7.74)
Unadjusted HR (95% CI) – ref MTX			
- Monotherapy	1.06 (0.97-1.16)	0.66 (0.43-0.99) †	1.03 (0.95-1.13)
- Sulfasalazine	0.98 (0.79-1.22)	1.10 (0.45-2.68)	0.99 (0.80-1.22)
- Leflunomide	1.18 (1.00-1.39)	0.88 (0.42-1.86)	1.16 (0.99-1.36)
- Two csDMARDs	0.94 (0.84-1.04)	1.08 (0.67-1.74)	0.94 (0.85-1.04)
- Three csDMARDs	0.95 (0.79-1.13)	1.23 (0.55-2.76)	0.96 (0.80-1.14)
Adjusted HR (95% CI) – ref MTX			
- Monotherapy	1.01 (0.91-1.12)	0.59 (0.35-0.97) †	0.99 (0.89-1.09)
- Sulfasalazine	1.01 (0.77-1.32)	1.77 (0.72-4.37)	1.04 (0.80-1.35)
- Leflunomide	1.16 (0.96-1.40)	0.85 (0.39-1.86)	1.14 (0.95-1.38)
- Two csDMARDs	0.93 (0.82-1.05)	1.15 (0.64-2.07)	0.94 (0.83-1.07)
- Three csDMARDs	0.97 (0.78-1.20)	1.15 (0.38-3.41)	0.98 (0.80-1.20)

TNF failure – adverse event			
Follow up (Person-years)	42876	1766	44642
No. of TNF patients with TNF inefficacy	3044	209	3253
Incidence / 100 patient years (95% CI)	7.10 (6.85-7.36)	11.83 (10.33-13.55)	7.29 (7.04-7.54)
Unadjusted HR (95% CI) – ref MTX			
- Monotherapy	1.21 (1.11-1.32) *	1.41 (1.02-1.96) †	1.23 (1.13-1.34) *
- Sulfasalazine	0.99 (0.79-1.23)	1.53 (0.68-3.44)	1.02 (0.82-1.26)
- Leflunomide	1.35 (1.15-1.59) *	1.38 (0.75-2.55)	1.36 (1.16-1.59) *
- Two csDMARDs	0.74 (0.66-0.83) *	0.82 (0.50-1.33)	0.74 (0.66-0.83) *
- Three csDMARDs	0.82 (0.68-1.00)	0.85 (0.37-1.93)	0.82 (0.68-1.00) †
Adjusted HR (95% CI) – ref MTX			
- Monotherapy	1.17 (1.06-1.30) *	1.64 (1.11-2.42) †	1.19 (1.08-1.32) *
- Sulfasalazine	1.11 (0.84-1.44)	1.42 (0.53-3.78)	1.11 (0.86-1.43)
- Leflunomide	1.36 (1.13-1.63) *	1.66 (0.85-3.24)	1.37 (1.15-1.64) *
- Two csDMARDs	0.85 (0.74-0.98) †	1.12 (0.65-1.93)	0.86 (0.75-0.98) †
- Three csDMARDs	1.02 (0.81-1.28)	0.67 (0.22-2.03)	1.00 (0.80-1.25)

*= p-value <0.01. † = p-value <0.05. Reference group = TNFi-Methotrexate combination. Adjusted for age, gender, disease duration, Rheumatic Disease Comorbidity Index, smoking, DAS28, HAQ-DI and steroid use

Table 19. BSRBR-RA cohort - exploratory analysis of TNFi discontinuation by age cut-off

Number of subjects	<65yrs (n=11,850)	≥65yrs (n=3,850)
TNF failure – all cause		
No. of patients	6098	2108
Incidence rate per 100 patient years (95% CI)	17.6 (17.1, 18.0)	21.3 (20.4, 22.2)
HZ (95% CI) (ref MTX): Unadjusted; Monotherapy	1.03 (0.97-1.10)	1.32 (1.19-1.47) *
Adjusted; Monotherapy	1.00 (0.93-1.08)	1.28 (1.13-1.44) *
TNF failure – inefficacy		
No. of patients	2581	761
Incidence rate per 100 patient years (95% CI)	7.4 (7.1, 7.7)	7.7 (7.2, 8.2)
HZ (95% CI) (ref MTX): Unadjusted; Monotherapy	1.00 (0.91-1.11)	1.16 (0.97-1.38)
Adjusted; Monotherapy	0.95 (0.84-1.07)	1.09 (0.89-1.34)
TNF failure – adverse events		
No. of patients	2295	958
Incidence rate per 100 patient years (95% CI)	6.6 (6.3, 6.9)	9.7 (9.1, 10.3)
HZ (95% CI) (ref MTX): Unadjusted; Monotherapy	1.10 (0.99-1.22)	1.49 (1.28-1.73) *
Adjusted; Monotherapy	1.08 (0.95-1.22)	1.45 (1.22-1.73) *

Number of subjects	<70yrs (n=13,777)	≥70yrs (n=1,923)
TNF failure – all cause		
No. of patients	7111	1095
Incidence rate per 100 patient years (95% CI)	17.8 (17.4, 18.2)	23.2 (21.9, 24.6)
HZ (95% CI) (ref MTX): Unadjusted; Monotherapy	1.08 (1.02-1.15) *	1.28 (1.11-1.48) *
Adjusted; Monotherapy	1.05 (0.98-1.12)	1.27 (1.07-1.50) *
TNF failure – inefficacy		
No. of patients	2968	374
Incidence rate per 100 patient years (95% CI)	7.4 (7.2, 7.7)	7.9 (7.2, 8.8)
HZ (95% CI) (ref MTX): Unadjusted; Monotherapy	1.05 (0.96-1.15)	0.96 (0.74-1.22)
Adjusted; Monotherapy	1.00 (0.90-1.12)	0.90 (0.67-1.22)
TNF failure – adverse events		
No. of patients	2739	514
Incidence rate per 100 patient years (95% CI)	6.9 (6.6, 7.1)	10.9 (10.0, 11.9)
HZ (95% CI) (ref MTX): Unadjusted; Monotherapy	1.17 (1.07-1.29) *	1.45 (1.18-1.79) *
Adjusted; Monotherapy	1.14 (1.02-1.27) †	1.48 (1.17-1.88) *

5.4 Discussion

To my knowledge this is the first study to investigate drug survival rates with TNFi monotherapy compared to TNFi/csDMARD combination therapy in older adults This work was published in *Rheumatology* in January 2020. In this large observational cohort of 15,000 patients, TNFi monotherapy is associated with an increase in treatment failure. However in older adults (≥75 years) the disadvantage of TNFi monotherapy on drug survival is no longer seen. This is explained by fewer discontinuations due to inefficacy, but a greater risk of discontinuations due to adverse events. This could be interpreted as evidence that monotherapy is more acceptable in the elderly. An alternative narrative would be that we are observing a phenomenon of 'competing risks', an elderly patient may suffer an adverse event leading to termination of therapy, which removes the patient from the 'risk pool' prior to the outcome of interest, in this case, loss of drug efficacy.

I also demonstrated significant differences between csDMARD combination strategies. The use of two csDMARDs with TNF blockade is associated with improved drug survival in the younger cohort. However, the cohort was overwhelmingly made up of patients receiving methotrexate and/or sulfasalazine. Leflunomide was less frequently used, but its presence either alone or in combination had a negative association with TNF inhibitor drug survival, irrespective of age groups.

There are several possible explanations for these findings. Crucially, the adverse event signal seen with TNFi monotherapy compared to TNFi/methotrexate combination therapy may be driven by channelling bias. Channelling is a form of selection bias seen in observational studies, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences (Petri and Urquhart, 1991). It is plausible that patients with a greater risk of adverse events are more likely to be

prescribed TNFi monotherapy which is presumed to have a better safety profile than combination therapy. To address for channelling bias in this cohort a propensity score model was created. The technique allows the comparison of non-randomised treatment strategies, adjusting for known covariates that may predict treatment decisions. Despite this, unmeasured confounding likely remains.

In the ≥75-year-old cohort, the lower incidence of failure due to inefficacy with TNFi monotherapy is interesting and potentially of clinical relevance. This may reflect my *a priori* hypothesis that there is a reduction in immunogenicity in this age group, as the aging immune system becomes less effective at mounting antibody responses, as phenomenon known as immunosenescence (Jani et al., 2014). Immunogenicity is a recognised mechanism underlying therapeutic failure with TNFi agents over time. Anti-drug antibodies are produced by the immune system in response to proteinaceous drugs, particularly monoclonal antibodies (Bartelds et al., 2011, Pascual-Salcedo et al., 2011). Concomitant use of methotrexate reduces the clearance of TNFi by lowering the incidence of anti-drug antibodies, resulting in a higher systemic exposure and improved drug survival. In the older cohort a reduction in immunogenicity may improve TNFi drug survival and preclude the need for concomitant methotrexate. In support of this immunosenescence hypothesis, the reduced risk of TNFi discontinuation due to inefficacy in patients receiving monotherapy was no longer apparent in the exploratory analyses using a younger age cut off of 65 and 70.

It is important to note that in my multivariate adjusted analyses, the imputed model demonstrated a statistically significant difference between the TNFi monotherapy and TNFi-methotrexate combination suggesting that the observed difference is not solely attributable to the measured confounders. However in imputed model including propensity score adjustment, the estimate was non-significant for

the over 75's, though the difference in the point estimate between the two models was negligible. A plausible explanation for this is that there is confounding by indication. It Is important to acknowledge that our adjustment model includes age and we may be including a path variable if our immunosenescence hypothesis is correct. It remains clear that age or some mechanism related to age is likely to be important in explaining the difference in effect of TNFi monotherapy versus combination therapy

The effect size (adjusted hazard ratio of 0·53) suggests patients ≥75 receiving TNFi monotherapy are nearly 50% less likely to discontinue TNFi due to inefficacy compared to patients receiving TNFi methotrexate combination. In part, this may be explained by the competing risk phenomenon; some patients who were destined to fail due to inefficacy experience an adverse event before meeting the inefficacy end point, thereby selecting themselves out of the 'at risk of inefficacy' cohort. Older patients are more likely to stop TNFi therapy than younger patients, and adverse events is the highest contributing reason for discontinuation. This may explain the slightly paradoxical finding that fewer older people stop due to inefficacy on monotherapy. The finding of higher discontinuation rates in the elderly is not surprising. Age is a consistent predictor for many outcomes that may lead to discontinuation, such as infection or cancer and direct drug toxicity.

My results are in keeping with published data from observational studies. The Dutch and Swiss registries reported comparable drug survival and reasons for discontinuations between the young and the elderly (Genevay et al., 2007, Radovits et al., 2009a), while the Italian registry demonstrated greater discontinuation in the elderly, with more frequent adverse events (Filippini et al., 2010). Zhang et al demonstrated that concomitant MTX improves persistence to biologic therapy in patients over 65 years, although analyses included patients <65 years old with certain disabilities, and no information was provided regarding reasons for discontinuation (Zhang et al., 2015). In contrast to earlier analyses

using BSRBR-RA data, I did not demonstrate inferiority of the sulfasalazine/TNFi combination (Soliman et al., 2011b). I did however confirm the association with leflunomide and lower TNFi treatment survival, which has also been demonstrated in the German registry, although this did not reach statistical significance (Strangfeld et al., 2009a).

This study has several strengths. The large sample size, limited missing data and accurate coding of treatment discontinuation has facilitated an in-depth and robust analysis. The BSRBR-RA includes data on elderly patients who are frequently excluded from clinical trials and provides real world data improving generalisability to clinical practice.

Despite the large overall sample size, the size of the ≥75-year cohort was relatively small, particularly in the 'inefficacy' model which limits statistical power. The decision to stop anti-TNF therapy and the reason for discontinuation was provided by the supervising rheumatologist, and I am unable to externally verify the accuracy of data provided. This may account for the number 'other' or 'missing' entrees, possibly introducing a degree of misclassification bias. All my analyses were based on csDMARD regimen at study entry. Patients may modify their csDMARD regimen after the introduction of TNFi. During the 5-year observation period, 18% of the cohort changed from their initial therapy choice of TNFi monotherapy, TNFi-methotrexate combination or TNFi-other csDMARD combination. Six percent of the cohort switched between TNFi monotherapy and TNFi-methotrexate combination. The proportion of 'switchers' was similar between the two age cohorts. I did not consider patients who switched between initial therapy choice in my analyses and this may have influenced TNFi survival. I chose to exclude previous csDMARD exposure from the multivariate model despite recognising this as an important confounder. This is because prior csDMARD therapy associates with the predictor variable (i.e. being on TNFi monotherapy is more likely to be associated with multiple failed csDMARDs). Lastly,

in this analysis I tested multiple hypotheses which potentially increases the chances of a false positive association, and as such these results should be interpreted with caution. Replicating these analyses in other registries' data and corroborating my results would prove invaluable.

In conclusion, these data provide evidence to support TNFi monotherapy strategies in the over 75. In the wider context of a desire to reduce polypharmacy burden, the findings in this study should help alleviate physician concerns about drug immunogenicity in older patients.

Chapter 6. Predictors of treatment non-response; the influence of co-morbidity and polypharmacy

This chapter examines the importance of co-morbidity and polypharmacy on treatment response and adverse events in patients receiving biological therapies within the BSRBR-RA. For patients with RA, the burden of comorbidity is high, and combined with the prescribing of multiple DMARDs, this cohort of patients are susceptible to increased polypharmacy. In these analyses each additional prescription for a comorbid condition reduced the odds of a good treatment response to biologics by 8%. Whilst each additional medication associated with an 13% increased risk of a serious adverse event. This results section has identified polypharmacy as a simple but valuable predictor of clinical outcomes in RA and supports medication count as a valid measure for use in epidemiologic analyses.

6.1 Introduction

Polypharmacy, the prescribing of multiple drugs for an individual, is rising in prevalence. Half of patients over 65 are prescribed 5 or more medications (Gao et al., 2018). This has quadrupled over the last 20 years (Gao et al., 2018), a consequence of an ageing population with comorbidities, and therapeutics advances with treatment guidelines advocating multiple medications. In treatment of RA prescribing of multiple DMARDs is advocated, with recommendation to commence combination therapy early (Smolen et al., 2017a, Ledingham, 2016, Singh et al., 2016b). Together with the day-to-day use of other medications to manage pain and counter side-effects, polypharmacy in this cohort is intensified. Despite dramatic improvements in the prognosis of RA, morbidity remains high (Gabriel and Michaud,

2009, Gonzalez et al., 2007). This is a consequence of the comorbidity burden which has increased considerably over recent decades (Nikiphorou et al., 2017), with an increased prevalence of cardiovascular disease, infections, malignancy and psychiatric illness (Listing et al., 2013, Smitten et al., 2008b, Solomon et al., 2006). Comorbidities are associated with worse quality of life and functional status (Dougados et al., 2013b), and are a confounder in analysis of clinical outcomes in RA (Michaud and Wolfe).

In epidemiological research, comorbidity indices select and weight illnesses to quantify collective burden. The choice of model depends upon patient population and outcome of interest. The Rheumatic Disease Comorbidity Index (RDCI) is composed of 11 weighted past or present comorbid conditions and performs well in predicting disease specific outcomes; including disability, medical costs, hospitalisation and death (Michaud and Wolfe, 2007, Wolfe, 2010, England et al., 2015). Comorbidity indices are reliant on accurate reporting, which is influenced by reporting methods i.e. physician versus patient (O'Malley et al., 2005). When correctly recorded, a binary code denotes the presence of a comorbidity but does not reflect its severity. Medication count and polypharmacy are gaining interest as surrogates of comorbidity burden. There has been an expansion in the use of real-world data captured from routine sources such as electronic health records (EHRs), where medication use is meticulously recorded (prescribing in UK primary care is almost exclusively electronic). EHRs have been utilised to support observational studies, as a stand-alone data source, or following linkage to administrative datasets (Cowie et al., 2017, Filkova et al., 2017).

The impact of polypharmacy on treatment outcomes in RA is largely unknown. As a surrogate for comorbidity, it may exert a similar effect. This would have important implications when making treatment decisions. From an epidemiological perspective, medication count may prove a valuable tool

in case mix adjustment. The primary objective of this study is to evaluate whether polypharmacy associates with treatment outcomes and serious adverse events (SAEs) in RA, and to establish whether polypharmacy represents a surrogate for comorbidity when adjusting for confounding in epidemiologic analyses.

6.2 Methods

Patient population:

Subjects were participants in the BSRBR-RA, a national prospective observational cohort study established in 2001 to monitor long-term safety of biological therapy. Ethics approval was granted in 2000 [MREC 00/8/053 (IRAS: 64202)]. All patients provided written informed consent. The BSRBR-RA methodology has been described previously (Watson et al., 2005). The data cut-off date was June 2016.

Baseline assessment:

Baseline data collected at registration included demographics, disease duration, DAS-28, DMARD and corticosteroid exposure, HAQ-DI, smoking status and comorbidity. Comorbidities were obtained from the patient's medical records, using a pre-specified list of coexisting conditions. Comorbidity burden was scored using the RDCI, which is superior to other common comorbidity indices in predicting death and physical disability (England et al., 2015).

Polypharmacy:

Medication count was recorded at study registration and defined by the total number of different medications prescribed concurrently. All regular and as-required medications were included. Non-prescribed medications (over-the-counter), topical and herbal/homeopathic medications were excluded. Polypharmacy was defined as a continuous variable and stratified into categories; ≤ 5, 6-9 or

≥ 10 medications. These cut-offs were selected a priori, based upon published literature to allow comparability (Jyrkka et al., 2011, Neutel et al., 2002, Gnjidic et al., 2012). Analyses were performed including and excluding synthetic DMARDs (not corticosteroids) in the medication count, with the best fit model described.

Follow-up:

Follow-up data were collected on a 6-monthly basis for the first 3 years by questionnaires sent to patients and their supervising rheumatology teams, and annually thereafter by questionnaires sent to the supervising rheumatology team only. Data on adverse events were captured from clinician questionnaires; from 6-monthly patient diaries detailing new hospital admissions, and by NHS-Digital which reported deaths

Outcome:

The first outcome was an improvement in RA disease activity defined as a 'good response' by the EULAR Improvement Criteria. Patients were classified into groups: no response, moderate response and good response, based on 12-month DAS-28 score. A good responder demonstrated an improvement in DAS-28 of at-least 1.2 units from baseline and an absolute score of <3.2 (van Gestel et al., 1998). Only patients commencing biologics were included in the analyses. Patients were excluded if they did not have a follow up within 12 months of starting their biologic.

The second outcome was SAE. This was defined as an adverse event coded by Medical Dictionary for Regulatory Activities terminology that resulted in death, hospitalisation or required intravenous therapy. Patient-reported SAE required verification by the supervising rheumatology team and completion of event-of-interest forms. All patients were included in the analyses and considered at risk until first SAE, death or last follow-up before 3 years, whichever came first. A single failure model was

used. Patients were allowed to contribute more than one event when comparing the type of adverse events across polypharmacy strata but only one event in the Cox model.

Statistical analysis:

Characteristics of patients in the strata of polypharmacy were tabulated and tested for statistically significant imbalance using Chi-square, Mann–Whitney or t-tests, as appropriate.

A logistic regression model was constructed to identify associations between polypharmacy and EULAR 'good response' at 12 months. Multivariable adjustment was made for age, gender, BMI, disease duration, baseline DAS-28, baseline HAQ, smoking status and RDCI. Odds ratios (OR) were recorded with corresponding 95% confidence interval (CI). Receiver Operator Characteristic (ROC) analyses were performed to compare the value of polypharmacy and RDCI in predicting EULAR response. Areas under the curve (AUC) were compared to investigate whether polypharmacy yielded significant advantages over RDCI.

To define SAEs, crude incidence rates per 100 patient-years with 95% confidence interval were calculated within each polypharmacy strata. Cox proportional hazards models were used to identify risk of SAE. Multivariable adjustment was made, as for the treatment response analysis plus glucocorticoids. The addition of corticosteroids in the model is because of its established strong link with SAEs. The utility of polypharmacy and RDCI in predicting SAE was evaluated using Cox proportional hazards models, and assumptions were tested graphically using Nelson-Aalen plots and Schoenfeld residuals. Best fit for both models was determined using Akaike's information criterion (AIC), Bayesian information criterion (BIC) and Harrell's C coefficient (measures the ordinal predictive power of a model). The models were tested with cross validation to assess generalisability to other independent datasets by determining the error rate. *K*-fold cross-validation was used, partitioning the full data set

into 5 approximately equal parts. P values of <0.05 were considered significant. As these analyses were exploratory, no correction for multiple hypothesis testing was made. Analyses were undertaken using Stata 14.

Missing data were addressed using multiple imputation. There were few baseline data missing (Table 20). Data on age, gender, number of medications and steroid use were complete. The primary variables analysed in the follow data were DAS-28 at 12 months. In the analyses of EULAR response at 12 months, patients were excluded if they were not on biologics (n=3,637) or if they did not have a follow up with 12 months of starting their biologic (n= 4376). This reduced the cohort to 16,470 patients. DAS28 was missing in 2634 patients. These data were considered missing at random. The missing baseline data and 12-month follow up DAS28 were imputed using multivariate sequential imputation using chained equations. Firstly, all missing values were filled in by simple random sampling with replacement from the observed values. The first variable with missing values, was regressed on all other variables. Missing values were replaced by simulated data points drawn from the corresponding posterior predictive distribution. Then, the next variable with missing was replaced by the same cycle. The imputation was 20 cycles, where at the end of the cycle one imputed dataset was created and the process was repeated to create 20 imputed datasets. The 20 datasets were combined using Rubin's rules therefore, the estimates and standard errors presented here are the combined ones. Results between the unimputed and imputed models were compared.

Table 20. BSRBR-RA cohort - missing data

Variable	Observations	Missing Variables
Analyses of EULAR response at 12 months (n=16470)		
Year onset of symptoms	16,264	206
Year of diagnosis	15,919	551
Seropositive	15,651	819
Erosive disease	15,959	511
Smoking status	16,141	329
BMI	13,392	3,078
Baseline DAS 28	16,345	125
Baseline HAQ	15,234	1,236
Follow up DAS at 12 months	13,836	2,634
Analyses of SAE (n=22,005)		
Year onset of symptoms	21,753	252
Year of diagnosis	21,280	725
Seropositive	21,051	954
Erosive disease	21,387	618
Smoking status	21,561	444
BMI	18,179	3,826
Baseline DAS 28	21,676	329
Baseline HAQ	19,629	2,376

6.3 Results

Patient characteristics:

22,005 subjects were registered in the BSRBR-RA. Eighty three percent were initiated on biologics, whilst 17% made up the comparison cohort. Baseline characteristics are Table 21. Mean age was 57, with median disease duration of 12 years. Baseline DAS-28 was 6.15 (SD 1.23), reflective of a biologic initiation cohort.

Polypharmacy and comorbidity:

Excluding RA medications, the median number of drugs prescribed was 5 (IQR 3 to 7). The highest number of prescribed drugs was 25. Sixty four percent of patients had ≤ 5 medications prescribed whilst 7% of patients had ≥ 10. Polypharmacy increased with age [r=0.26, p<0.0001]. Half of patients over 65 were prescribed 5 or more medications, which is in keeping with the population average (Gao et al., 2018). While there was no difference in the median number of drugs between genders (median number of drugs [interquartile range]; female 4 [3-6] and male 4 [3-7], p=0.16), the imbalance tests revealed a significant difference across the polypharmacy strata. Specifically, compared to females, males were more likely to be prescribed ten or more medications. Current smokers were taking fewer medications than non-smokers [5.7 ± 2.8 versus 6.0 ± 2.9, p = <0.0001]. Polypharmacy was associated with higher baseline HAQ scores [r=0.26, p<0.0001] (Table 21).

The most prevalent comorbidity was cardiovascular disease, with hypertension the commonest condition. There was a history of diabetes in 7% and angina, myocardial infarction or stroke in 9% of patients. A history of cancer including basal cell, was found in 5%. The median RDCI score was 1 (IQR 0 to 2). Six percent had a RDCI score of 4 or more. Medication count correlated with the RDCI comorbidity index (r 0.41, p<0.001) (Table 22).

Table 21. BSRBR-RA cohort - baseline characteristics by polypharmacy strata

	Total	Medication			Stat. imbalance
		≤ 5	6-9	≥ 10	(Kwallis * or $\chi^{2\,\dagger}$)
Number	22,005	14,105	6,452	1,448	
Age (year) *	57 (12)	55 (13)	60 (11)	63 (10)	0.0001*
Sex, female	16,678 (76%)	10,678 (76%)	4,944 (77%)	1,056 (73%)	0.01 †
BMI (mg/m2) †	27 (23-30)	26 (23-29)	27 (24-31)	28 (25-33)	0.0001*
Smoker - current	4,652 (22%)	3,218 (23%)	1,204 (19%)	230 (16%)	< 0.001†
- past smoker	8,336 (39%)	4,863 (35%)	2,790 (44%)	683 (49%)	
RDCI score †	1 (0-2)	0 (0-1)	1 (1-2)	3 (2-4)	0.0001*
Seropositive (RF)	13,312 (63%)	8,529 (63%)	3,999 (65%)	784 (59%)	< 0.001 †
Disease duration †	10 (4-18)	9 (4-16)	12 (5-20)	12 (6-21)	0.0001*
Steroid user	8,324 (38%)	4,103 (29%)	3,349 (52%)	872 (60%)	< 0.001†
Erosions (hand/feet x-ray)	11,689 (55%)	7,499 (54%)	3,499 (56%)	691 (51%)	0.05 †
Baseline DAS28 *	6.15 (1.23)	6.10 (1.25)	6.25 (1.20)	6.23 (1.19)	0.0001*
Baseline HAQ *	1.88 (0.68)	1.77 (0.70)	2.05 (0.59)	2.19 (0.53)	0.0001*

All values are gives as number (%) unless otherwise specified. * Mean (SD). † Median [p25-p75]. Erosion on hand or feet x-ray defined as present or absent by clinician at baseline.

Table 22. BSRBR-RA cohort – the correlation of baseline variables (Rho, p value)

	Drug count	RDCI	Age	Gender	BMI	Smoke	Seropositive	Disease Duratio	Steroid User	Erosive	Baseline DAS28	Baseline HAQ
Drug count	1											
RDCI	0.44 0.00	1										
Age	0.26 0.00	0.25 0.00	1									
Gender	0.01 0.27	-0.03 0.00	-0.07 0.00	1								
BMI	0.15 0.00	0.17 0.00	0.01 0.25	-0.04 0.00	1							
Smoke	-0.01 0.19	-0.06 0.00	-0.02 0.04	0.16 0.00	0.01 0.27	1						
Seropositive (RF)	0.01 0.07	0.00 0.79	0.03 0.00	-0.01 0.28	-0.03 0.00	-0.07 0.00	1					
Disease duration	0.12 0.00	0.08 0.00	0.18 0.00	0.04 0.00	-0.08 0.00	0.08 0.00	0.06 0.00	1				
Steroid User	0.31 0.00	0.05 0.00	0.06 0.00	-0.06 0.00	0.00 0.81	-0.01 0.34	0.02 0.03	0.08 0.00	1			
Erosive	0.02 0.01	-0.02 0.03	0.04 0.00	0.00 0.66	-0.10 0.00	0.01 0.10	0.24 0.00	0.28 0.00	0.01 0.43	1		
Baseline DAS28	0.08 0.00	0.01 0.45	-0.01 0.37	0.05 0.00	0.00 0.66	-0.01 0.18	0.07 0.00	0.07 0.00	0.08 0.00	0.07 0.00	1	
Baseline HAQ	0.27 0.00	0.16 0.00	0.13 0.00	0.13 0.00	0.07 0.00	-0.03 0.00	0.06 0.00	0.21 0.00	0.14 0.00	0.09 0.00	0.39 0.00	1

Polypharmacy as a predictor of RA disease activity

16,346 patients had follow-up within 12 months of starting their biologic. Data for calculation of EULAR response were available for 13,834 patients (85%). All analyses presented are based upon the imputed model (Table 23). The unimputed (complete case) data are presented after (Table 24). A model excluding DMARDs from total medication count was used. Each additional DMARD improved the chances of good EULAR response in contrast to each additional non-DMARD which had an inverse effect.

The mean change in DAS-28 from baseline to 12 months was 2.28 (SD 1.6). A moderate EULAR response was seen in 50% and a good EULAR response in 31%. There were statistically significant decreased odds of good EULAR response in the higher polypharmacy strata compared to patients taking ≤5 medications. For each additional medication prescribed, there was an 8% reduction in the likelihood of achieving a good response at 12 months. Adjusting for age and gender attenuated the association marginally. This remained statistically significant after a third adjustment using RDCI as a confounder, and in the multivariable analyses. A sensitivity analysis including DMARDs in the medication count demonstrated lower odds ratios [unadjusted OR 0.95 (95% CI 0.94 to 0.96), $p<0.001$] which did not remain statistically significant in multivariable analysis.

Table 23. BSRBR-RA cohort – imputed logistic regression model analysis examining the association between polypharmacy and treatment response

	Polypharmacy strata (excluding DMARDs)		
	≤ 5	6-9	≥ 10
Total patients	10,268	4,978	1,100
Change in DAS28 at 12 months (SD)	2.37 (1.6)	2.17 (1.6)	2.01 (1.6)
EULAR response			
- No response	18%	21%	24%
- Moderate response	49%	54%	53%
- Good response	34%	25%	23%
	Odds ratio (95% CI) by strata (excluding DMARDs)		
Unadjusted	Ref	0.67† (0.62, 0.72)	0.60† (0.51, 0.70)
Adjusted			
- age and sex	Ref	0.71† (0.66, 0.77)	0.65† (0.55, 0.76)
- age, sex, RDCI	Ref	0.77† (0.71, 0.84)	0.78* (0.65, 0.92)
- age, sex, RDCI, smoker, BMI, disease duration, baseline DAS28 and HAQ	Ref	0.86† (0.79, 0.94)	0.93 (0.77, 1.11)
	Odd ratio (95% CI) of total number of drugs		
	Excluding DMARDs	Including DMARDs	
Unadjusted polypharmacy	0.92† (0.91, 0.93)	0.95† (0.94, 0.96)	
Adjusted			
- age and sex	0.94† (0.92, 0.95)	0.96† (0.95, 0.98)	
- age, sex, RDCI	0.95† (0.94, 0.97)	0.98* (0.97, 1.00)	
- age, sex, RDCI, smoker, BMI, disease duration, baseline DAS28 and HAQ	0.98* (0.96, 1.00)	1.01 (0.99, 1.02)	
	Odd ratio (95% CI) of DMARDs-only medication count		
Unadjusted polypharmacy	1.37† (1.31, 1.43)		
Adjusted			
- age and sex	1.33† (1.27, 1.39)		
- age, sex, RDCI	1.32† (1.26, 1.38)		
- age, sex, RDCI, smoker, BMI, disease duration, baseline DAS28 and HAQ	1.26† (1.21, 1.32)		

† = p<0.001, * = P<0.01.

Table 24. BSRBR-RA cohort - complete case logistic regression model analysis examining the association between polypharmacy and treatment response

	Polypharmacy strata (excluding DMARDs)		
	≤ 5	6-9	≥ 10
Total patients	10,268	4,978	1,100
Change in DAS28 at 12 months (SD)	2.40 (1.6)	2.20 (1.6)	2.07 (1.6)
EULAR response			
- No response	17%	20%	23%
- Moderate response	48%	54%	53%
- Good response	35%	26%	24%
	Odds ratio (95% CI) by strata (excluding DMARDs)		
Unadjusted	Ref	0.67† (0.62, 0.73)	0.59† (0.50, 0.69)
Adjusted			
- age and sex	Ref	0.72† (0.66, 0.78)	0.64† (0.55, 0.76)
- age, sex, RDCI	Ref	0.77† (0.71, 0.84)	0.77* (0.65, 0.91)
- age, sex, RDCI, smoker, BMI, disease duration, baseline DAS28 and HAQ	Ref	0.88# (0.79, 0.98)	0.93 (0.75, 1.15)
	Odd ratio (95% CI) of total number of drugs		
	Excluding DMARDs	Including DMARDs	
Unadjusted polypharmacy	0.92† (0.91, 0.93)	0.95† (0.94, 0.96)	
Adjusted			
- age and sex	0.93† (0.92, 0.94)	0.96† (0.95, 0.98)	
- age, sex, RDCI	0.95† (0.93, 0.96)	0.98* (0.97, 1.00)	
- age, sex, RDCI, smoker, BMI, disease duration, baseline DAS28 and HAQ	0.98 (0.96, 1.00)	1.01 (0.99, 1.03)	
	Odd ratio (95% CI) of DMARDs-only medication count		
Unadjusted polypharmacy	1.37† (1.31, 1.43)		
Adjusted			
- age and sex	1.33† (1.27, 1.39)		
- age, sex, RDCI	1.32† (1.26, 1.38)		
- age, sex, RDCI, smoker, BMI, disease duration, baseline DAS28 and HAQ	1.27† (1.20, 1.34)		

† = p<0.001, * = P<0.01.

Polypharmacy as a predictor of serious adverse events

All analyses presented are based upon the unimputed model (Table 25). The imputed data are presented after (Table 26). There was no meaningful difference in point estimates between the complete case and imputed analyses. A model excluding DMARDs from total medication count was used.

During a 3 year follow up period from registration, there were 12,547 SAEs in 7,286 patients. Crude IRs were greater in ascending polypharmacy strata. Infection was the most frequent SAE, and the proportion of SAEs due to infection increased in ascending strata [≤5 medication 27%; 6-9 medications 29%; and ≥10 medication 31%, p=0.001]. Adverse drugs reactions contributed to 0.1% of all SAEs. There were 24 recorded ADR; overdose (accidental) (n=13), drug toxicity (n=2), medication error (n=1) and drug intolerance (n=8). Of these 24 ADR, 12 were recorded as SAEs.

There was a statistically significant increased risk of SAE in higher polypharmacy strata (Table 25). For each additional medication there was a 13% increase risk of SAE. This remained statistically significant after adjustment using RDCI and in multivariable analysis. The association between number of medication and SAEs was non-linear (Figure 20).

Over time, the proportion of patients in each polypharmacy strata at year of registration to BSRBR-RA has remained relatively stable (Figure 21). Adjustment for year of registration did not numerically affect the hazard ratio. For each additional medication there was still a 10% increase risk of SAE [age, sex and registration year adjusted HR 1.10 (95% CI 1.10 to 1.11), p<0.001]. This remain statistically significant after a fourth adjusting using comorbidity [age, sex, registration year & RDCI adjusted HR 1.08 (95% CI

1.07 to 1.09), p<0.001] and in the multivariate analysis [adjusted HR 1.06 (95% CI 1.05 to 1.07), p<0.001].

Table 25. BSRBR-RA cohort - incidence rate and Cox proportional hazard estimates for complete case analysis examining the association between polypharmacy (excluding DMARDs) and serious adverse event

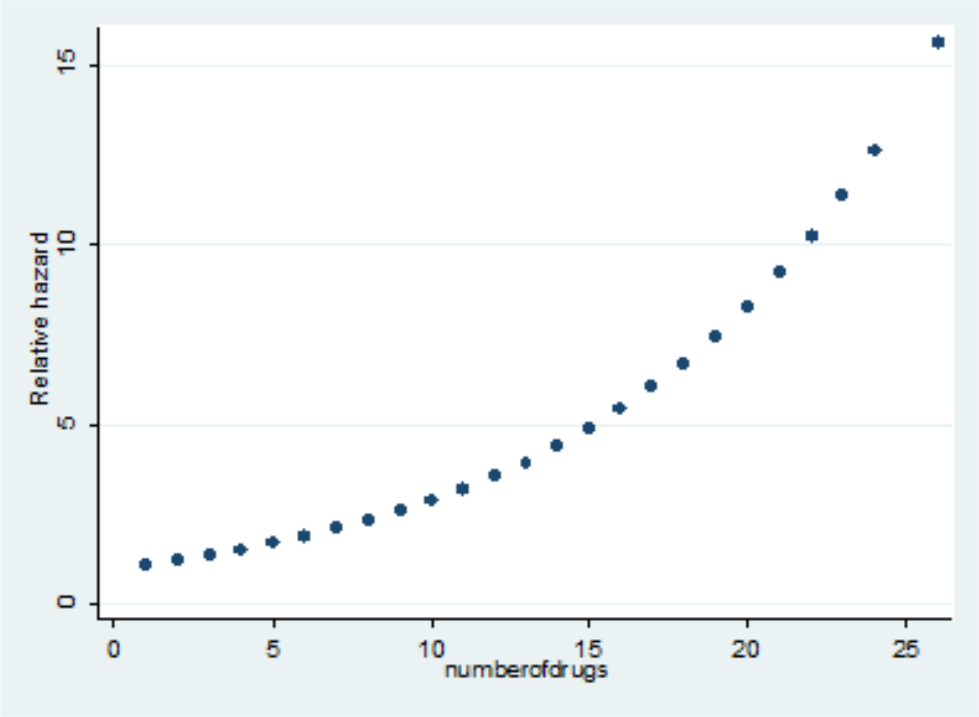
	Medication			Total
	≤ 5	6-9	≥ 10	
Total patients	14,105	6,452	1,448	22,005
Patients with at least 1 SAE	3,887	2,667	732	7,286
Number of SAEs	6,099	4,933	1,515	12,547
Incidence rate				
Exposure time (Person-years)	34,089	15,679	3,282	53,051
Failures (No. of admissions)	6,099	4,933	1,515	12547
Incidence / 100 years (95% CI)	17.9	31.5	46.2	23.7
	(17.4-18.3)	(30.6-32.4)	(43.9-48.5)	(23.2-24.1)
Hazard ratio (95% CI) by polypharmacy strata				
Unadjusted polypharmacy	Ref	1.76† (1.70, 1.83)	2.62† (2.48, 2.77)	
Adjusted				
- age and sex	Ref	1.54† (1.49, 1.60)	2.11† (2.00, 2.24)	
- age, sex and RDCI	Ref	1.47† (1.41, 1.53)	1.97† (1.86, 2.09)	
- age, sex and steroid	Ref	1.42† (1.36, 1.47)	1.74† (1.63, 1.85)	
- age, sex, RDCI, steroid smoker, BMI, dis dur, DAS28 /HAQ	Ref	1.27† (1.21, 1.33)	1.49† (1.38, 1.61)	
Hazard ratio (95% CI)				
Unadjusted	1.13† (1.12, 1.13)			
Adjusted				
- age and sex	1.10† (1.09, 1.11)			
- age, sex and RDCI	1.09† (1.09, 1.10)			
- age, sex and steroid	1.08† (1.07, 1.08)			
- age, sex, RDCI, steroid smoker, BMI, dis dur, DAS28 /HAQ	1.06† (1.05, 1.07)			

† = p<0.001

Table 26. BSRBR-RA cohort - Cox proportional hazard estimates for imputed analysis examining the association between polypharmacy (excluding DMARDs) and serious adverse event

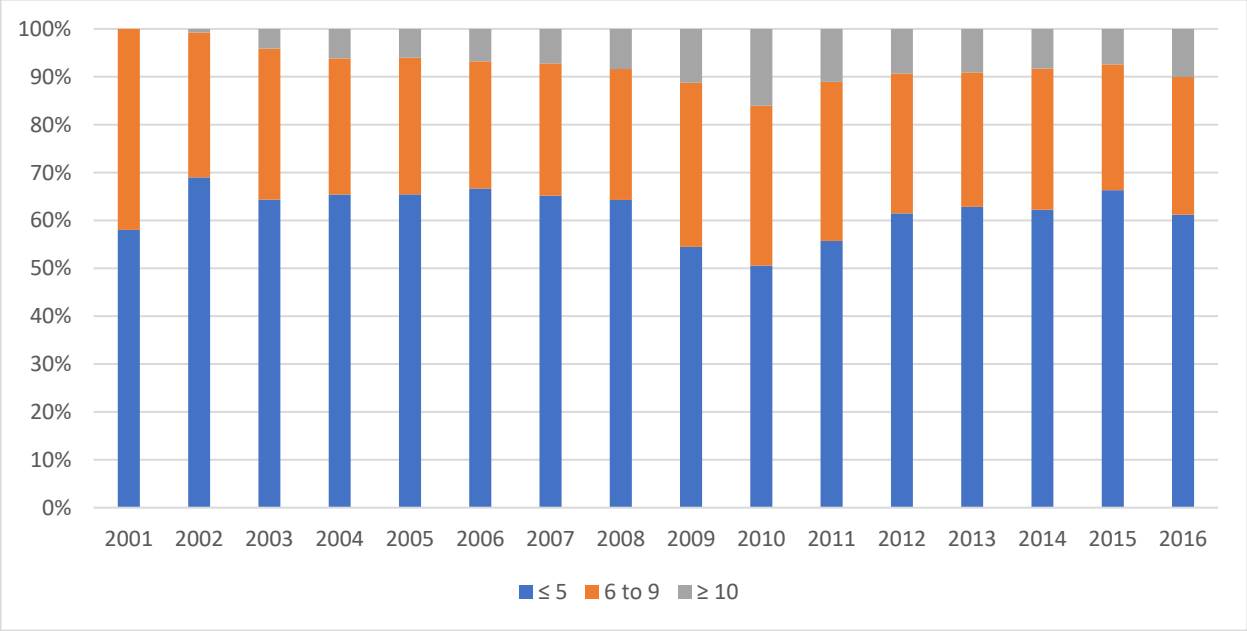
	Medication		
	≤ 5	6-9	≥ 10
Hazard ratio (95% CI) by polypharmacy strata			
Unadjusted	Ref	1.76† (1.70, 1.82)	2.59† (2.44, 2.74)
Adjusted			
- age and sex	Ref	1.55† (1.49, 1.61)	2.09† (1.97, 2.21)
- age, sex and RDCI	Ref	1.46† (1.41, 1.52)	1.94† (1.83, 2.05)
- age, sex and steroid	Ref	1.42 (1.36, 1.47)	1.72† (1.62, 1.83)
- age, sex, RDCI, steroid smoker, BMI, dis dur, DAS28 /HAQ	Ref	1.38† (1.33, 1.44)	1.77† (1.70, 1.88)
Hazard ratio (95% CI)			
Unadjusted	1.13† (1.12, 1.13)		
Adjusted			
- age and sex	1.10† (1.09, 1.10)		
- age, sex and RDCI	1.09† (1.08, 1.10)		
- age, sex and steroid	1.08† (1.07, 1.08)		
- age, sex, RDCI, steroid smoker, BMI, dis dur, DAS28 /HAQ	1.08† (1.07, 1.08)		

Figure 20. BSRBR-RA cohort – polypharmacy associated with a marked nonlinear increase in risk in SAE



This graph demonstrates the associated between increasing number of prescribed medications and relative hazard for serious adverse event.

Figure 21. BSRBR-RA cohort – the proportion of patients in polypharmacy strata at year of registration



This stacked bar graph demonstrates the proportion of patients in each polypharmacy strata by year of registration to the BSRBR-RA which has remained relatively stable over time.

A sensitivity analysis including DMARDs in total number of drugs demonstrated numerically lower IR and hazard ratios. As expected, there were a higher proportion of patients in the higher polypharmacy strata (≥ 10 medication including DMARDs: n= 2596, 12% cohort, compared to ≥ 10 medication excluding DMARDs: n = 1,448, 6% cohort). This resulted in a lower incidence of SAE in the higher polypharmacy strata. In the DMARDs-included analysis, there were 2534 SAE over 5966-person years in the ≥10 medication strata, compared to the DMARDs excluded analysis, where there were 1515 SAEs over 3,282-person years. In the Cox proportional hazards model, the hazard rates were numerically lower in the DMARDs-included analysis. For each additional medication there was an 11% increase risk of SAE [age/sex adjusted HR 1.11 (95% CI 1.10 to 1.12), p<0.001]. This remain statistically significant after adjustment using comorbidity [age, sex & RDCI adjusted HR 1.06 (95% CI 1.06 to 1.07), p<0.001]. In the fully adjusted model, the HR was similar to the DMARD–excluded analysis; DMARDs-included [adjusted HR 1.05 (95% CI 1.04 to 1.06), p<0.001]; DMARDs-excluded [adjusted HR 1.06 (95% CI 1.05 to 1.07), p<0.001] (Table 27).

A further sensitivity analysis excluding corticosteroids from the total number of drugs demonstrated similar finding. In the Cox proportional hazards model, the hazard rates were similar to that seen in the primary analysis which included steroids in the polypharmacy count. For each additional medication there was an 12% increase risk of SAE. In the adjusted model the HR was identical to the steroid-included analysis; age, sex & steroid adjusted [HR 1.09 (95% CI 1.09 to 1.10), p<0.001] and fully adjusted [HR 1.05 (95% CI 1.04 to 1.06), p<0.001] (Table 28).

Table 27. BSRBR-RA cohort - Cox proportional hazard estimates in sensitivity analysis examining association between polypharmacy including DMARDs and serious adverse events

	Medication			Total
	≤ 5	6-9	≥ 10	
Total patients	10,724	8,685	2,596	22,005
Patients with at least 1 SAE	2947 (27%)	3086 (36%)	1253 (48%)	7286
Number of SAEs	4631	5382	2534	12547
Proportion of infective SAE	1242 (27%)	1529 (28%)	773 (31%)	3544 (28%)
Incidence rate				
Exposure time (Person-years)	26,025	21,060	5,966	53,051
Failures (No. of admissions)	4631	5382	2534	12547
Incidence / 100 years (95% CI)	17.7	25.6	42.5	23.7
	(17.2, 18.3)	(24.9, 26.2)	(40.9, 44.2)	(23.2, 24.1)
Hazard ratio (95% CI) by polypharmacy strata				
Unadjusted	Ref	1.45† (1.39, 1.50)	2.43† (2.32, 2.55)	
Adjusted	Ref	1.31† (1.26, 1.36)	1.98† (1.89, 2.08)	
- age and sex				
- age, sex and RDCI	Ref	1.25† (1.20, 1.30)	1.83† (1.74, 1.93)	
- age, sex and steroid	Ref	1.22 (1.17, 1.27)	1.64† (1.55, 1.73)	
- age, sex, RDCI, smoker, BMI, dis dur, DAS28 /HAQ	Ref	1.10† (1.05, 1.16)	1.42† (1.33, 1.52)	
Hazard ratio (95% CI)				
Unadjusted	1.11† (1.10, 1.12)			
Adjusted				
- age and sex	1.08† (1.08, 1.09)			
- age, sex and RDCI	1.08† (1.07, 1.08)			
- age, sex and steroid	1.06† (1.06, 1.07)			
- age, sex, RDCI, smoker, BMI, dis dur, DAS28 /HAQ	1.05† (1.04, 1.06)			

Table 28. BSRBR-RA cohort - Cox proportional hazard estimates in sensitivity analysis examining association between polypharmacy excluding corticosteroids and serious adverse events

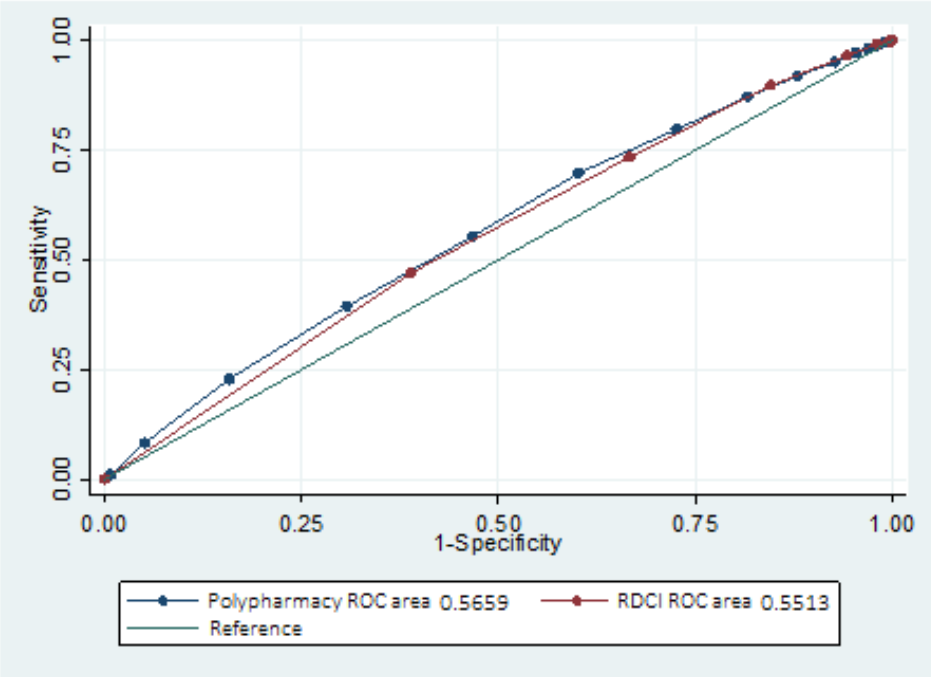
	Medication		
	≤ 5	6-9	≥ 10
Hazard ratio (95% CI) by polypharmacy strata			
Unadjusted	Ref	1.76† (1.70, 1.83)	2.31† (2.17, 2.45)
Adjusted			
- age and sex	Ref	1.53† (1.47, 1.59)	1.93† (1.82, 2.05)
- age, sex and RDCI	Ref	1.49† (1.44, 1.55)	1.95† (1.83, 2.08)
- age, sex and steroid	Ref	1.38† (1.32, 1.43)	1.59† (1.49, 1.96)
- age, sex, RDCI, smoker, BMI, dis dur, DAS28 /HAQ	Ref	1.28† (1.22, 1.35)	1.54† (1.42, 1.67)
Hazard ratio (95% CI)			
Unadjusted	1.12† (1.11, 1.13)		
Adjusted			
- age and sex	1.10† (1.09, 1.10)		
- age, sex and RDCI	1.09† (1.09, 1.10)		
- age, sex and steroid	1.07† (1.07, 1.08)		
- age, sex, RDCI, smoker, BMI, dis dur, DAS28 /HAQ	1.06† (1.05, 1.07)		

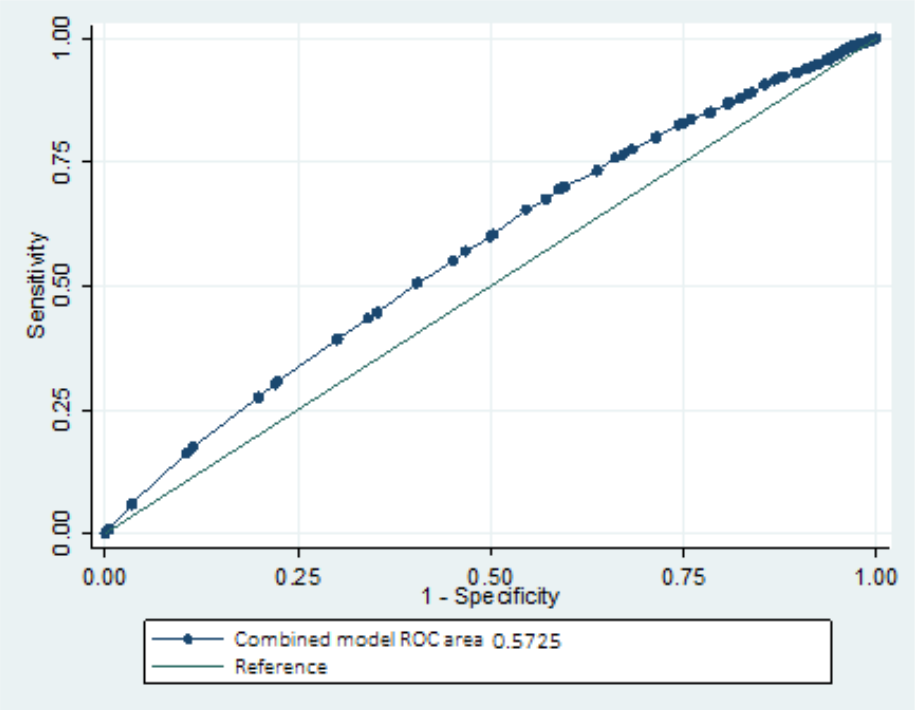
Comparing polypharmacy and comorbidity in predicting disease response and SAEs

ROC analyses estimating the diagnostic accuracy of polypharmacy and RDCI as predictors of RA disease activity demonstrated a similar AUC, although the polypharmacy model was statistically greater [AUC 0.57 for polypharmacy and 0.55 for RDCI, $p<0.007$]. Combining models yielded an AUC of 0.57, and fully adjusted AUC of 0.67 (Figure 22).

In the SAE analysis, neither the polypharmacy or RDCI model diagnostics violated the assumption of proportionality for the Cox hazard model. Akaike's information criterion and Bayesian information criterion were numerically lower for polypharmacy, although it was not meaningful to conclude a superior model fit. Harrell's C coefficient was numerically similar for both models: polypharmacy = 0.59 (0.58–0.60) and RDCI = 0.58 (0.57–0.58). The models were cross validated in the dataset to assess generalizability. For polypharmacy and RDCI, prediction errors were similar: Harrell's C coefficient polypharmacy = 0.58 and RDCI = 0.58 (Table 29).

Figure 22. BSRBR-RA cohort - receiver operating characteristic (ROC) analysis comparing the diagnostic accuracy of polypharmacy and RDCI in predicting RA disease activity





These figures demonstrate the area under the curve (AUC) investigating any advantage from the polypharmacy model over the RDCI model in prediction of RA disease activity. Whilst demonstrating similar AUC, the polypharmacy model was statistically greater [AUC 0.57 for polypharmacy and 0.55 for RDCI, $p<0.007$]. Combining both models yielded an AUC of 0.57.

Table 29. BSRBR-RA cohort - analysis comparing the 'best fit model' comparing polypharmacy and RDCI in predicting SAEs

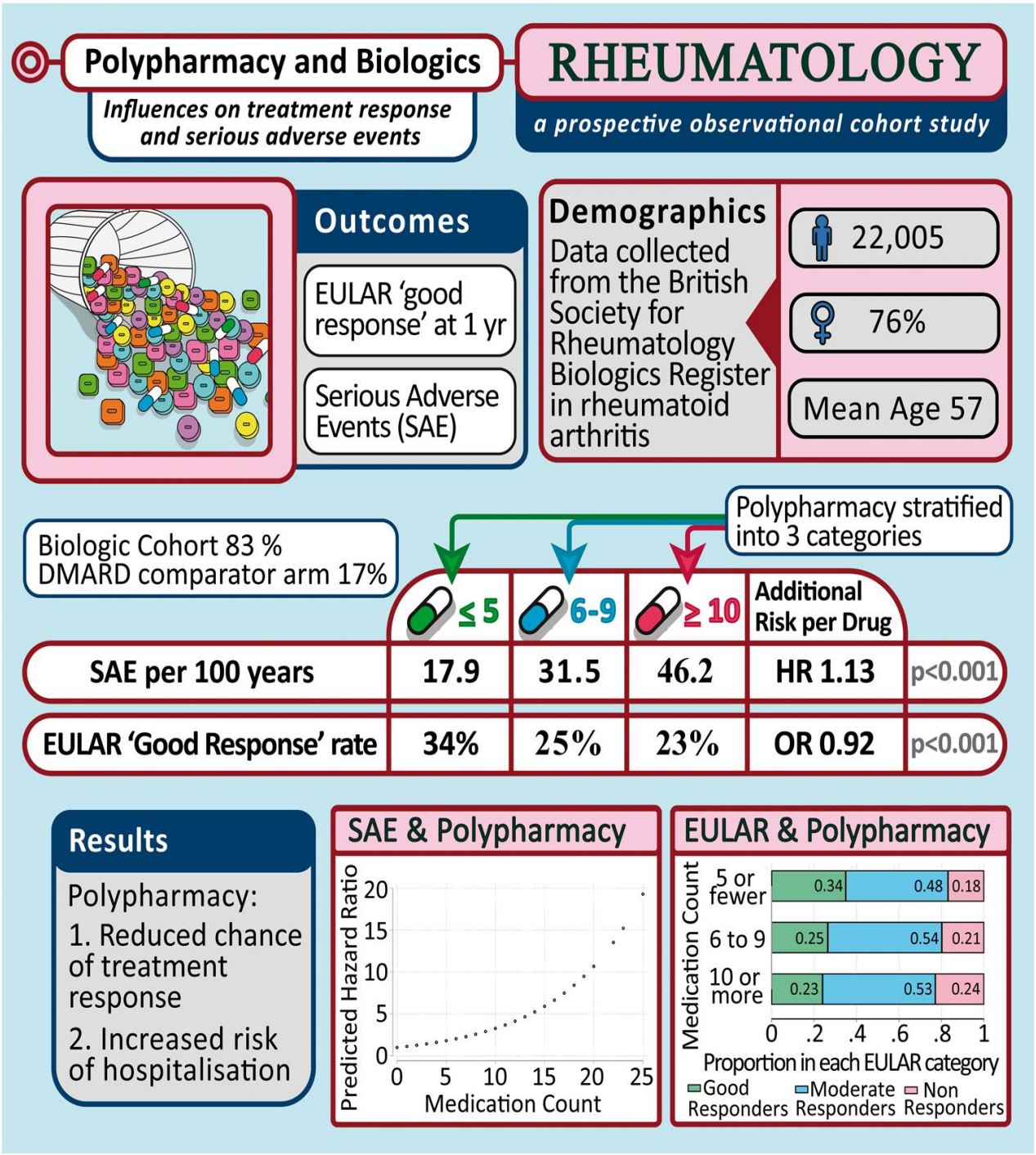
	Polypharmacy model			
	HR (95% CI)	AIC	BIC	Harrell's C
Unadjusted	1.13[†] (1.12, 1.13)	232914[b]	232924[b]	0.59 (0.58-0.60)
Adjusted				
- age and sex	1.10[†] (1.09, 1.11)	231706[b]	231736[b]	0.62 (0.62-0.63)
- age, sex, disease duration, baseline DAS28 and HAQ	1.08[†] (1.08, 1.09)	200258[b]	200318[b]	0.63 (0.63-0.64)
- age, sex, smoker, BMI steroid, disease dur, DAS28 /HAQ	1.08[†] (1.08, 1.09)	163728[b]	163827[b]	0.63 (0.63-0.64)

	RDCI model			
	HR (95% CI)	AIC	BIC	Harrell's C
Unadjusted	1.26[†] (1.24, 1.27)	233386	233396	0.58 (0.57-0.58)
Adjusted				
- age and sex	1.19 (1.17, 1.20)	232064	232094	0.62 (0.61-0.62)
- age, sex, disease duration, baseline DAS28 and HAQ	1.17 (1.15, 1.18)	200413	200473	0.63 (0.62-0.64)
- age, sex, smoker, BMI steroid, disease dur, DAS28 /HAQ	1.17 (1.15, 1.19)	163798	163896	0.63 (0.62-0.64)

	Combined model		
	HR (95% CI)	AIC	BIC
Unadjusted	1.10 (1.09, 1.10)	232621[b]	232641[b]
Adjusted			
- age and sex	1.08 (1.07, 1.09)	231547[b]	231587[b]
- age, sex, disease duration, baseline DAS28 and HAQ	1.06 (1.06, 1.07)	200122[b]	200192[b]
- age, sex, smoker, BMI steroid, disease dur, DAS28 /HAQ	1.06 (1.05, 1.07)	163603[b]	163711[b]

[b] Best fit, lower AIC value demonstrates better model fit; [b] Best fit, lower BIC value demonstrates better model fit

Figure 23. BSRBR-RA cohort - visual abstract representation of analyses (Bechman et al 2019)



6.4 Discussion

To my knowledge this is the first study to describe the association between polypharmacy and treatment response and is the largest analysis quantifying polypharmacy and SAEs in RA. It was reported in *Rheumatology* in October 2019. In this large observational cohort I have described a strong magnitude of association between polypharmacy and clinical outcomes. The more medications a patient is receiving in addition to their rheumatic disease medication, the less likely they are to achieve a clinically meaningful disease improvement. Whilst increasing medication count, irrespective of concomitant DMARDs use, is strongly associated with an increased risk of SAEs.

After adjusting for an individual's comorbidity burden, medication count retained a residual effect on EULAR response and SAEs, although the magnitude is greater for SAEs. There are two possible explanations for this. Firstly, medication count may capture a distinct facet of the same construct captured by comorbidity. Whilst the RDCI defines comorbidities in a binary fashion, medication count provides increased granularity about comorbidity severity. Consider two patients with heart failure, one receiving ACE-inhibition alone, the other on triple therapy with ACE-inhibition, beta-blockade and a diuretic. These patients would have equivalent RDCI scores, however their medication count would reflect the differing severity of disease. Medication count includes preventive as well as therapeutic medications, which permits the identification of a cohort at high risk for future illness. This is not detected by routine comorbidity indices and may explain the persistent SAE signal after adjustment for RDCI. Increasing polypharmacy may also reflect more severe RA, with additional medications required to manage pain, counteract drug side effects and treat associated comorbidities (Au et al., 2011).

The other explanation is that polypharmacy may have a direct effect on treatment response and SAEs. This is hard to explain from a pharmacokinetic perspective. I evaluated treatment response to biologics

which are not metabolised via cytochrome P450 or cleared by renal elimination, and thus unlikely to be altered by concomitant medications which influence these pathways. It is plausible that polypharmacy is implicated in the causal pathway of SAEs. Adverse drug reactions (ADRs) account for 6.5% of all hospital admissions (Bourgeois et al., 2010, Kongkaew et al., 2008, Pirmohamed et al., 2004), and have increased by 50% over the last decade (Veeren and Weiss, 2017). In a prospective secondary care study, polypharmacy was the only independent predictor of ADRs admissions, with each additional medication increasing the risk by 14% (Davies et al., 2009). In my analyses ADRs made up a very small proportion of overall adverse events. If polypharmacy is a direct causal factor in hospitalisation through ADRs, its effect is likely small and unlikely to influence its efficacy as an epidemiological tool.

The association between corticosteroid use and SAEs, particularly infection, is well recognised. Adjusting for steroid use, the effect of medication count on SAEs was slightly reduced but remained significant. It was not appropriate to include DMARDs in the medication count when analysing outcomes. As expected, each additional DMARD improved the chance of treatment response. This is not a novel observation (Soliman et al., 2011a), and supports continued use of background DMARD combinations for patients on biologic therapy. In the SAE analysis, there was a greater risk with each additional medication excluding DMARDs than including DMARDs; unadjusted 13% versus 11%. This supports a protective property of DMARDs against SAEs, which has been previously reported (Smitten et al., 2008a). This may reflect improved RA disease activity (Au et al., 2011) or the prescribing of less aggressive immunosuppression to patients perceived at high infection risk.

Few studies have examined polypharmacy in RA. In the general population, polypharmacy is a common finding in hospitalised patients (Nobili et al., 2011) and a predictor of unplanned admissions (Payne et al., 2013), especially in the elderly (Cherubini et al., 2012, Beer et al., 2011), where it performs superiorly in predicting health care costs and utilisation over comorbidity indexes (Perkins et al., 2004,

Farley et al., 2006). Treharne et al quantified polypharmacy in a secondary care RA cohort, and identified a significant correlation between polypharmacy and comorbidity (Treharne et al., 2007). In cross-sectional analyses, polypharmacy correlates with DAS-28, although this has not been replicated (Gonzalez-Gamboa et al., 2016). Filkova et al demonstrated similar results in a secondary care cohort as presented here, with a nonlinear association between polypharmacy and hospitalisations, and a 2.5x risk of hospitalisation for patients prescribed ≥10 medications (Filkova et al., 2017).

Future research is warranted on medication optimisation in RA, which could consider whether polypharmacy is deemed appropriate (Gallagher et al., 2008, Avery et al., 2011, Panel, 2015). It would be valuable to examine the complexity of a medication regimen, which is an independent risk factor for poor outcomes, and a better predictor of mortality than polypharmacy in older patients (Wimmer et al., 2016). Stratifying medications according to their subclasses might help identify the differential impact of drugs within polypharmacy. When considering medication count one must recognise the impact primary non-adherence. 5-20% of UK primary care prescriptions are not redeemed (Beardon et al., 1993, Fischer et al., 2010). Polypharmacy therefore reflects the number of medications a patient clinically requires, but not the true number consumed.

This study has several strengths. As highlighted in previous chapters, the BSRBR-RA provides real world data, with generalisability to clinical practice. Large sample size, limited missing data and accurate coding of medications, comorbidities, DAS-28, and SAEs has facilitated an in-depth and robust analysis.

There are limitations to this study. The BSRBR-RA cohort was skewed towards those with severe disease requiring biologics (80% of patients recruited started a biologic) and therefore SAE analyses may not fully represent routine care. In the treatment response analyses I only examined response to biologics and cannot assume these findings translate to patients managed on conventional synthetic DMARDs

alone. The number of SAEs are higher than routine care. This might be explained by my methodology, where I limited the analysis period to the first 3 years post BSRBR-RA registration. This 3 year cut off was chosen as data collection after this period was less robust. It is recognised that risk of SAE, especially infection, in patients who commence biologics is not constant over time and greatest early on, especially the first 6 months of therapy (Galloway et al., 2011). The prevalence of comorbidity was similar to that reported in the general RA population (Dougados et al., 2013b, Hyrich et al., 2006a), although channelling bias may have contributed to a healthier subset of patients who are likely to be referred for biologics over higher risk candidates. Lastly, the cumulative impact of treatment recommendations from multiple clinical guidelines has contributed to vast changes in polypharmacy over time (Beardon et al., 1993, Fischer et al., 2010). Adjustment for year of registration did not numerically affect the hazard of SAE. However it is still possible that the usefulness of polypharmacy as a surrogate for comorbidity is time specific and influenced by contemporary guidelines.

In conclusion polypharmacy represents a simple but valuable predictor of clinical outcomes in patients with RA. In clinic a medication count can help physicians personalise care; for every additional medication a patient is taking after their DMARD therapy, they are 8% less likely to achieve a good treatment response when starting a biologic and have an 13% increased risk of experiencing a SAE. It would be wrong to conclude that this is a direct causal link and that reducing polypharmacy will modify these risks, although further research is warranted to explore this question. This study supports medication count as a valid measure, readily extracted from routine care datasets for case mix adjustment in epidemiologic analyses.

Chapter 7. Adverse events on biological DMARDs; non-serious infections in the BSRBR-RA

This chapter addresses the third and final aim of this thesis, examining treatment related adverse events, in particular non serious infections (NSI) in patients receiving biological therapies. Patients with RA are at an increased risk of infection. However, historically serious infections have received the most attention in research literature and are only the tip of the iceberg. NSI are far more frequent, and although not life-threatening, have potential to impact treatment outcomes and quality of life. In these analyses there is a high frequency of reported NSI, affecting 1 in 8 patients each year. The risk factors for developing a non serious events are comparable to those observed in patients with serious infections. Biologics are associated with an increased risk of NSI, with the greatest risk seen with tocilizumab. Whilst unmeasured confounding must be considered, the magnitude of effect is large, and it is likely that a causal link between NSI and targeted immunosuppression exists. Further research is needed to understand the impact of NSI on clinical outcomes including drug survival and quality of life.

7.1 Introduction

Patients with RA experience a greater number of infections compared to the background population. These infections are frequent, can be severe, and contribute to substantial morbidity and mortality (Doran et al., 2002a, Wolfe et al., 1994, Cobb et al., 1953, Franklin et al., 2007b). Infection susceptibility is likely a combination of disease related immunological dysfunction, immunocompromising comorbidities and the use of immunomodulatory drugs.

The risk of serious infections, defined as an infection that is life-threatening or requiring hospitalization or intravenous antibiotics, has been the main focus of in long-term clinical trial extension studies and observational drug registries. cs-DMARDs have relatively little impact (Lacaille et al., 2008, Doran et al., 2002b, Bernatsky et al., 2007), whilst corticosteroids consistently demonstrate a dose dependant risk (Dixon et al., 2011c, Franklin et al., 2007a, Strangfeld et al., 2011b, Crowson et al., 2012, Dixon et al., 2012). Observational cohorts have compared the rates of serious infection across cytokine and targeted immune cell blocking agents. Biologics are associated with a small but significant risk of serious infection (Galloway et al., 2011, Listing et al., 2005, Curtis et al., 2007, Askling et al., 2007b). Differences in risk are observed between biologics agents, which have particular clinical relevance in 'high risk' individuals (Rutherford et al., 2018c, Listing et al., 2005, Askling et al., 2007b).

Serious infections are the tip of the iceberg. NSI defined as those events managed outside of a hospital admission, have been reported in 20-30% of RA patients each year (Doran et al., 2002a, Au et al., 2011) and are the most common adverse events in large clinical trials. In elderly RA patients, rates of NSI are estimated at 47.5 per 100 patient-years (Dixon et al., 2011a). Although these events are not life-threatening, their burden may be high (Dao et al., 2012b). Recurrent NSI leads to treatment discontinuation (Pan et al., 2009). Meta-analyses of data on immune-mediated inflammatory diseases have suggested differences in the risk of NSI between TNFi (Dao et al., 2012b).

Despite extensive literature on infection in RA, data on non-serious events are limited. To my knowledge, there has been little research into what predicts an NSI in patients with RA, and the extent to which immunomodulatory drugs influence this risk. The primary objective of this study was to describe the frequency and pattern of NSI and compare the incidence of NSI between biologic drug within the British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA).

7.2 Methods

Patient population:

Study subjects were participants in the BSRBR-RA, a national prospective observational cohort study established in 2001 to monitor long-term safety of biological therapy. Initial biologic cohorts were for etanercept and infliximab users. Adalimumab, rituximab, tocilizumab and certolizumab-pegol cohorts were recruited in 2004, 2008 and 2010, respectively, whilst JAK inhibitors (tofacitinib and baricitinib) and sarilumab cohorts have been recruited from 2017/2018. Abatacept and golimumab cohorts were not recruited. The BSRBR-RA methodology has been described previously (Watson et al., 2005). Ethics approval was granted in 2000 [MREC 00/8/053 (IRAS: 64202)]. The data cut-off date for this study was January 2019.

Baseline assessment

Data collected at registration included demographics, disease duration, smoking status, comorbidity, DMARD and corticosteroid exposure, DAS28-ESR, HAQ-DI scores and comorbidities (yes/no) from a list. For analysis, comorbidity burden was scored using the Rheumatic disease comorbidity index (RDCI) (Wolfe and Michaud, 2010).

Follow-up:

Follow-up data were collected on a 6-monthly basis for the first 3 years through questionnaires sent to patients and their supervising rheumatology teams, and annually thereafter by questionnaires sent to the supervising rheumatology team only. Data on adverse events were captured from clinician questionnaires; from 6-monthly patient diaries and by linkage to NHS Digital which provides mortality

data. Patients diaries were provided for the first 3 years, where patients were asked to record details of all new prescriptions (including antibiotics) and hospital attendances. Patient-reported serious adverse events required verification by the supervising rheumatology team. No additional verification of non-serious adverse events occurred but all reported NSI were recorded in the database and coded.

Outcome:

The primary outcome was an NSI reported to the BSRBR-RA by either the clinical team or the patient. This was defined as an infectious episode that did not require hospitalisation, intravenous therapy, or lead to severe disability or death recorded by either the hospital or the patient. Infections were coded by the Medical Dictionary for Regulatory Activities terminology.

Exposure:

Individuals were considered 'at risk' from the date of commencing their first registered biologic treatment for up to 3 years, or until date of treatment discontinuation, last received follow-up or death, whichever came first. Censorship at three years was aligned to the time frame when diaries where collected, which was a key source of NSI. Patients could stop or switch therapies during the 3-year period and all biologic exposure during this 3-year window was included. A switch to another biologic during this time would not extend the total follow up window past 3 years as diary collection terminated 3 years after registration; for example, if a patient started a subsequent biologic after 2 years, they would only contribute a maximum of 1 year to this second biologic.

Due to BSRBR-RA study design hospitals had the option of "re-registering" existing study patients with the BSRBR-RA at the point of them switching to a therapy which was actively recruiting. For example, a

patient recruited in 2003 at the point of starting etanercept could then re-register in 2012 with a new study identification number when starting a new biologic. All subsequent follow-up time would be transferred to the new study ID, but the two IDs would be linkable in the dataset. This facilitated a capture of updated baseline data contemporaneous to the new registration and increased the frequency of follow-up and restart diary capture for a further 3 years. Therefore, patients could enter the study on multiple occasions and contribute a further 3 years of time to the analysis.

To allow for ongoing exposure risk from the biologic's half-life after stopping therapy, an additional 90 days of exposure time was considered for all biologics apart from rituximab, where an additional 180 days of exposure time was considered, although in all cases censored at the maximum 3 year cut-off.

Statistical analysis:

Crude incidence rates per 100 patient-years with 95% confidence interval were calculated. A multiple-failure Cox proportional hazards model was used to compare risk of NSI across groups, since many patients experienced multiple events. A traditional (single-failure) model examining time to first event would ignore any additional infections overlooking important information to enable us to understand risk. We therefore used a multiple failure model, allowing patients to contribute more than one event, where dependency in the hazard function was modelled as a shared frailty (i.e. random effect). Cluster robust estimates for confidence intervals were calculated. The risk of NSI were compared across biologic cohorts and reported as hazard ratios.

TNFi was chosen as the reference for comparison as it was the most widely used class of drug in the register. For analyses within the TNFi class, etanercept was used as the reference for comparison.

Biosimilar use was not considered different from originator use and all continuous exposure to the "same" drug was combined. Golimumab, abatacept, tofacitinib and baricitinib were excluded from the analyses as the number of patients receiving these medications was low or absent.

Potential confounders were selected *a priori* based upon clinical knowledge and available variables. Adjustments included age, gender, DAS28, HAQ-DI, disease duration, smoking, baseline steroid usage and year recruited to the BSRBR-RA. Line of biologic therapy, referring to the number of different biologics subsequently prescribed over the three-year period was included as a time varying co-variate. To account for competing risks and to adjust for clustering of events within individuals, the number of cumulative serious and non-serious infections were also included as time varying co-variates. Assumptions of the Cox model were tested using Nelson-Aalen plots.

Missing data were addressed using multiple imputation with chained equations for 20 cycles. The predictor data on biologic exposure were near complete. Of the 288,828 lines of data, only one line was missing data on biologic exposure. There were missing data for several baseline variables used in the multivariate analysis. Data on age, gender, comorbidity, steroids at baseline and entry year were complete. Missing data are presented below (Table 30). All missing data were imputed regardless of the reason or reasons it was missing. The following variables with complete data were utilised for the imputation: age; gender; comorbidity; steroid use, current DMARDs exposure and year of entry. The data were imputed using multivariate sequential imputation using chained equations. All missing values were filled in by simple random sampling with replacement from the observed values. Linear and logistic regression were performed to impute the normally distributed and dichotomous variables respectively. The first variable with missing values, was regressed on all other variables. The imputation was 20 cycles, where at the end of the cycle one imputed dataset was created and the process was

repeated to create 20 imputed datasets. The 20 datasets were combined using Rubin's rules so the estimates and standard errors presented are the combined ones. Results between the unimputed and imputed models were compared. Analyses were undertaken using Stata 15 (StataCorp., College Station, TX, USA).

Sensitivity analyses:

Analyses using different drug exposure windows, limiting to 'on drug time only' (excluding the 3-or 6-month half-life exposure risk) and also extending to an 'ever exposed' model until point of switch were compared. To account for the effect of serious infection, sensitivity analyses were performed incorporating serious infection as a competing risk using the Fine & Gray method (Fine and Gray, 1999). To account for patients who registered a second time within the BSRBR-RA and contributed to more than one drug cohort, we recalculated standard errors using the cluster robust sandwich estimator, accounting for the within person correlation across these different observations.

Table 30. BSRBR-RA cohort - missing data

Variable	Observations at baseline	Missing Variables
Entire cohort (n=23,584)		
Disease duration	23,235	349
DAS28-ESR	22,685	899
HAQ	20,503	3,081
Smoking status	22,129	1,455
Cohort with no prior biologic (n=19538)		
Disease duration	19,290	248
DAS28-ESR	18,857	681
HAQ	17,195	2,343
Smoking status	19,277	261

7.3 Results

Patient characteristics

A total of 23,584 individual patients were registered in the BSRBR-RA until January 2019. The baseline characteristics are listed in Table 31. The mean age was 57 years and the median disease duration was 10 years. The median baseline DAS28 was 6.10 (5.29-6.91) reflective of a biologic initiation cohort. Less than 5% of the cohort (n=1174) registered a second time within the BSRBR-RA and contributed more than one episode to the analysis.

Eighty three percent of the cohort were biologic naïve at registration. The first biologic received during the 3-year period was a TNFi in 74%. This comprised etanercept 32%, adalimumab 20%, infliximab 17%, and certolizumab 5%. Of these patients, 88% were started on a TNFi originator. The remaining patients were prescribed either an IL-6 inhibitor (4.4%) (tocilizumab (4.3%) or sarilumab (0.1%)), rituximab (5.3%) or continued off biologics as part of the csDMARD comparison cohort (14.8%). Patients receiving JAK inhibition or anakinra were excluded from the analyses. Of those starting therapy, 46.6% (n=9898) switched to a second agent during their 3 year follow up.

Patients were asked to return a diary every 6 months during follow-up. Diaries were received from 15,205 of 23,584 patients (64.5%). Of patients who returned a diary during the first three years (the exposure window for the Cox models) 63% returned more than 2/3rd of their diaries whilst 16% returned fewer than 1/3rd of diaries. Diary return was slightly lower amongst the IL-6 cohort and amongst smokers (Table 32).

Table 31. BSRBR-RA cohort - baseline characteristics by biologic DMARD cohort

	BSRBR-RA population	Biologic cohort			
		No Biologic	TNFi	IL-6	B-Cell (Rituximab)
Total Number of patients	23,584	3481	17,487	1,025	1.255
Age (year) *	56.6 (12.9)	60.0 (12.5)	55.6 (13.0)	57.6 (12.1)	59.4 (12.1)
Sex, Female, n (%)	17,319 (73.4)	2,534 (72.8)	12,776 (73.1)	799 (78.0)	959 (76.4)
Smoker (%) - current	4,701 (21.2)	811 (23.5)	3,318 (21.0)	133 (17.7)	182 (21.6)
- ex-smoker	8,438 (37.8)	1,392 (40.4)	6,305 (37.5)	279 (37.2)	347 (41.3)
RDCI score †	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)
- Cardiovascular disease, n (%)	1,975 (8.4)	427 (12.3)	1,252 (7.2)	101 (9.9)	169 (13.5)
- Respiratory disease, n (%)	3,799 (16.1)	661 (19.0)	2,609 (14.9)	207 (20.2)	272 (21.7)
Disease duration (years) †	10 (4 to 18)	6 (1 to 15)	10 (5 to 18)	10 (5 to 19)	12 (6 to 20)
Steroid use as baseline, n (%)	8,151 (34.6)	804 (23.1)	6,398 (36.6)	311 (30.3)	511 (40.7)
Concurrent DMARD use, n (%)					
- No DMARDs	4,806 (20.4)	29 (0.8)	4,131 (23.6)	275 (26.8)	234 (18.7)
- Methotrexate only	8,813 (37.4)	1,224 (35.2)	6,487 (37.1)	397 (38.7)	610 (48.6)
- Sulfasalazine only	1,080 (4.6)	448 (12.9)	551 (3.2)	31 (3.0)	37 (3.0)
- Leflunomide only	1,144 (4.9)	266 (7.7)	761 (4.4)	39 (3.8)	64 (5.1)
- Hydroxychloroquine only	547 (2.3)	79 (2.3)	379 (2.2)	44 (4.3)	32 (2.6)
- Other DMARD only	657 (2.8)	162 (4.7)	443 (2.5)	11 (1.1)	36 (2.9)
- Two DMARDs	5,115 (21.7)	996 (28.6)	3,700 (21.2)	186 (18.2)	185 (14.7)
- Three or more DMARDs	1,416 (6.0)	275 (7.9)	1,031 (5.9)	42 (4.1)	57 (4.5)
Baseline DAS28 †	6.10 (5.29 to 6.91)	5.15 (4.32 to 6.03)	6.29 (5.51 to 7.05)	5.73 (5.05 to 6.50)	6.11 (5.38 to 6.83)
- TJC	13 (7 to 20)	7 (3 to 12)	14 (8 to 21)	12 (7 to 19)	13 (8 to 20)
- SJC	8 (4 to 13)	5 (2 to 8)	9 (5 to 14)	6 (4 to 10)	8 (4 to 12)
- PGA	73 (54 to 84)	55 (40-75)	75 (60-85)	75 (60-84)	73 (56-83)
- ESR	34 (18 to 57)	29 (16-48)	36 (19-59)	25 (10-46)	36 (20-62)

	BSRBR-RA population	Biologic cohort			
		No Biologic	TNFi	IL-6	B-Cell (Rituximab)
Baseline CRP	20 (7 to 46)	18 (7-42)	21 (8-49)	12 (5-35)	21 (8-45)
Baseline HAQ †	2 (1.38 to 2.38)	1.63 (1 to 2.13)	2 (1.5 to 2.38)	1.88 (1.38 to 2.25)	2.13 (1.63 to 2.38)
First biologic drug to patient (%)	19,538 (82.8)	-	15,199 (86.9)	232 (22.6)	262 (20.9)

All values are gives as number (%) unless otherwise specified. * Mean (SD). † Median [p25-p75]. Abbreviations: RDCI, Rheumatic Disease Comorbidity Index; Respiratory = COPD and asthma. Cardiovascular = IHD/CVA, Seropositive for rheumatoid factor; DAS28, Disease Activity Score 28 Joints; HAQ-DI, Health Assessment Questionnaire Disability Index. Due to study design, hospitals had the option of "re-registering" existing study patients with the BSRBR-RA at the point of them switching to a therapy which was actively recruiting patients. This occurred with 1174 patients, 5% of the total cohort.

Table 32. BSRBR-RA cohort - proportion of patients returning diaries

	Patients who retuned at least 1 diary during 3 year follow up period	Of the patients whom returned diaries, percentage that returned >2/3rd of that required
Entire cohort	15,205 (64.5%)	70.4%
By smoking		
- non smoker	6134 (68.2%)	65.8%
- ex-smoker	5723 (67.8%)	64.0%
- current smoker	2707 (57.6%)	58.2%
By drug cohort		
- TNFi	11,420 (65.3%)	63.6%
- Anti-IL-6R	465 (45%)	40.4%
- Anti-CD20	795 (63.4%)	64.4%
- csDMARDs	2428 (69.8%)	65.6%

Non serious infection (NSI)

There were 17,304 non-serious infective episodes in 8145 patients during the 3 year follow up period (Table 33). The median number of infections per patient was 1, interquartile range 1-3. Respiratory infections accounted for 36% of all NSI. Urinary, ENT (ear nose and throat) and skin infections were the next most frequently reported. Non-serious opportunistic infections were reported, with herpes zoster (n=224) and candidiasis (n=373) being the most frequent.

Limited to the time on drug during the first three years of follow-up (the exposure window for the Cox models), there were 27.0 NSI events per 100 patient years of follow-up (95%CI 26.6 to 27.4) in the multi-failure model (Table 34). Using a single failure model, there were 12.7 events per 100 patient years of follow-up (95%CI 12.4 to 12.9), indicating 12.7% patients reported an NSI each year. Increasing age, female gender, comorbidity burden, corticosteroid therapy, higher RA disease activity (defined by the DAS28) and more disability (recorded by the HAQ-DI score) were associated with an increased risk of NSI. Compared to never smokers, current smokers had a lower risk of NSI. Patients recruited into the BSRBR-RA in more recent years also had a lower NSI risk

Table 33. BSRBR-RA cohort – class of non-serious infections

			Limited to 3 years (exposure window for Cox model) *more than 1 type of infection could be listed for same event
Total number of recorded NSI			17,602
Person years			64,034.
Patients with infection			8145
Number of infections /patients			(IQR 1-3, max 26)
-	Respiratory		6,268
-	Urinary		2,921
-	ENT		2,486
-	Skin		1,850
-	Oral		791
-	Musculoskeletal		744
-	Gastrointestinal		277
-	Ocular		482
-	Genital		143
-	Neurological		2
-	Other		1,638
-	Sinusitis		593
-	Influenza		137
-	Herpes Zoster		224
-	Bacterial:	Tuberculous	2
		NTM[†]	0
		Legionellosis	0
		Pseudomonas	6
		Listeria **	0
		Salmonellosis **	3
-	Viral:	Herpes zoster	224
		Herpes simplex **	55
		Cytomegalovirus disease	1
		HIV	0
		HBV reactivation	0
		PML	0
-	Fungal:	Candidiasis **	373
		PJP	0
		Aspergillus **	2
		Actinomycosis	1
-	Parasite:	Cryptosporidium	0
		Strongyloidiasis **	0

[†] NTM includes avium complex, xenopi, fortuitum.

** Candida, aspergillus, listeria, salmonella, herpes simplex, strongyloides only considered an indictor infection if the infection is invasive or disseminate. This information is not available in the BSRBR-RA dataset.

Non serious infection risk by biologic:

The incidence of NSI by biologic class and within TNFi class is shown in Table 34. Anti-IL-6R (28.3 cases per 100 patient years) had a higher risk of NSI than TNFi in both the complete case and imputed adjusted model [adjusted hazard ratios 1.42 (95% CI 1.27 to 1.60) P <0.001], whilst the biologic-naive cohort on csDMARD alone had a lower risk of infection (19.2 cases per 100 patient years) [adjusted HR 0.64 (95% CI 0.59 to 0.72) P <0.001] (Table 34 and Figure 24). Rituximab (33.6 cases per 100 patient years) had a higher risk of NSI than TNFi [unadjusted HR 1.15 (95% CI 1.02, 1.29) P=0.02]. In the multivariate analysis with imputation, the HR remained significantly increased. The unadjusted, complete case adjusted and imputed adjusted HRs are all shown in table 3. Each biologic was associated with a greater risk of NSI when compared to the biologic-naive cohort on csDMARD alone (Table 35).

Within the TNFi class, the largest cohort was etanercept which was set as the reference group. In both unadjusted and adjusted models, adalimumab had a higher risk of NSI than etanercept [adj HR 1.10 (95% CI 1.04, 1.16*)* P = 0.001]. In the unadjusted model, compared to etanercept, infliximab had a higher risk of NSI whilst certolizumab had a lower risk, although this did not remain statistically significant in multivariable analysis (Table 34 and Figure 25). Results between the unimputed and imputed analyses were compared. Hazard estimates were increased in the imputed model. There were no changes in direction of estimates.

Table 34. BSRBR-RA cohort - incidence rate and Cox proportional hazard estimates of NSI comparing biologic exposure

Incidence rate / 100 patient yrs (95% CI)	Incidence rate	No. infections	Follow up (Person-yrs)
Population	27.0 (26.6, 27.4)	17,304	64,035
Incidence rates by treatment			
- csDMARDs	19.2 (18.5, 19.9)	3016	15715
- TNFi	29.4 (28.9, 29.9)	12280	41752
- Anti-IL-6R	28.3 (26.3, 30.5)	688	2428
- Anti-CD20	33.6 (31.8, 35.6)	1179	3504
Incidence rates: TNFi treatment			
- Infliximab	33.7 (32.5, 34.9)	3097	9190
- Etanercept	27.4 (26.7, 28.2)	4995	18217
- Adalimumab	31.3 (30.3, 32.3)	3763	12023
- Certolizumab	18.4 (16.7, 20.3)	416	2259

Hazard ratio (95% CI)	
Age (by decade)	1.03 (1.01, 1.05) *
Gender (ref male)	1.61 (1.51, 1.71) **
Smoking (ref never smoker): former	1.01 (0.95, 1.07)
current	0.81 (0.76, 0.87) **
Disease duration (by year)	1.01 (1.01, 1.01) **
RDCI	1.11 (1.09, 1.13) **
Steroids	1.25 (1.19, 1.32) **
DAS28	1.15 (1.13, 1.17) **
HAQ	1.35 (1.30, 1.40) **
Year of entry into BSRBR	0.95 (0.94, 0.95) **
Non serious infection during time period	1.46 (1.42, 1.51) **
Line of therapy	1.13 (1.09, 1.18) **

Treatment Hazard ratio (95% CI)			
Biologic exposure (ref TNFi)			
Unadjusted	-	Anti-IL-6R	0.96 (0.84, 1.10)
	-	Anti-CD20	1.15 (1.02, 1.29) †
	-	csDMARDs	0.66 (0.62, 0.71) *
Adjusted	-	Anti-IL-6R	1.32 (1.15, 1.52) **
	-	Anti-CD20	1.15 (0.97, 1.36)
	-	csDMARDs	0.66 (0.60, 0.72) **
Imputed Adjusted	-	Anti-IL-6R	1.42 (1.27, 1.60) **
	-	Anti-CD20	1.28 (1.14, 1.43) **
	-	csDMARDs	0.64 (0.59, 0.69) **

Treatment Hazard ratio (95% CI)

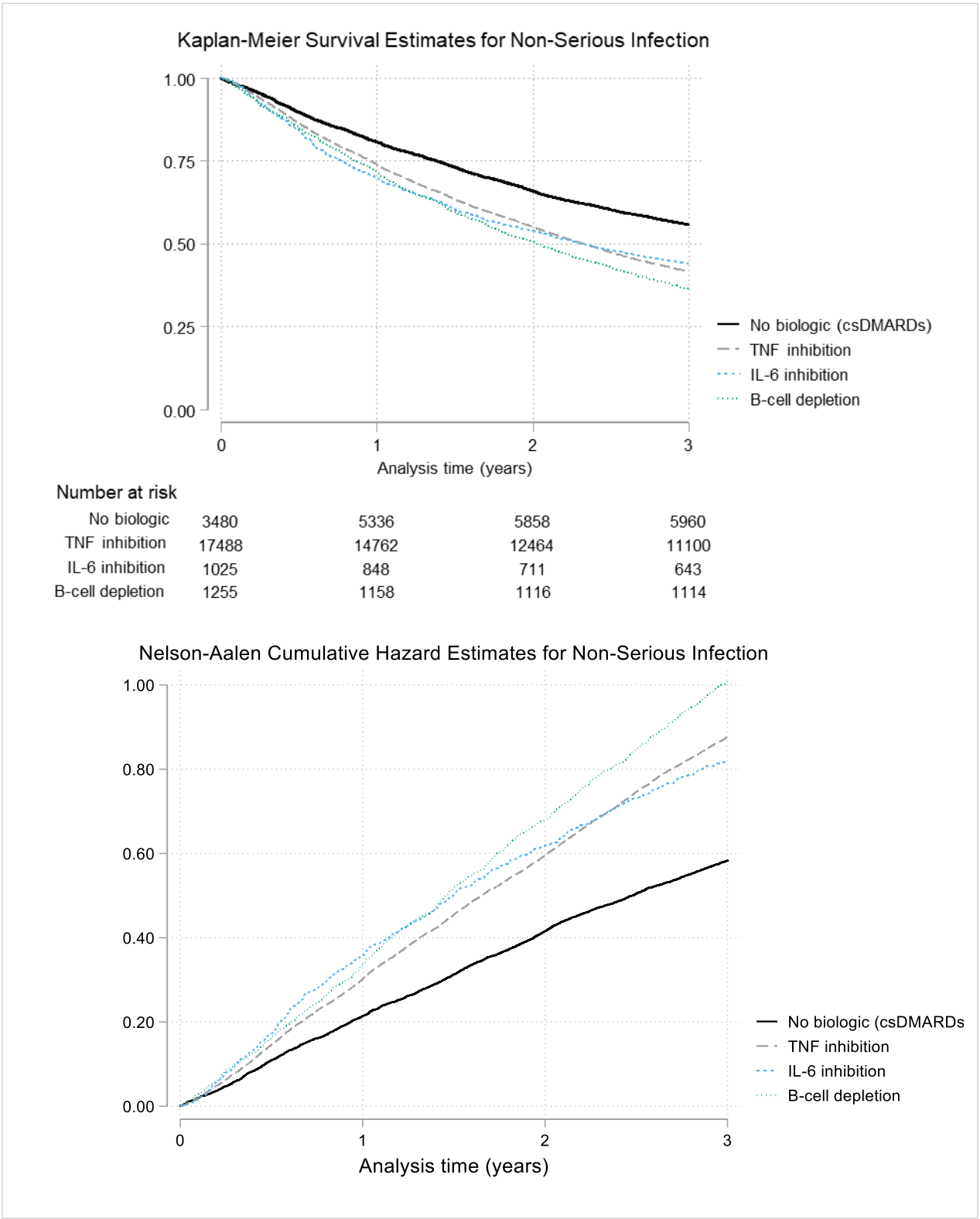
TNF class exposure (ref Etanercept)			
Unadjusted	-	Infliximab	1.22 (1.14, 1.31) **
	-	Adalimumab	1.14 (1.07, 1.22) **
	-	Certolizumab	0.67 (0.58, 0.78) **
Adjusted	-	Infliximab	1.01 (0.93, 1.08)
	-	Adalimumab	1.10 (1.04, 1.16) *
	-	Certolizumab	1.14 (0.97, 1.35)
Imputed Adjusted	-	Infliximab	1.00 (0.93, 1.07)
	-	Adalimumab	1.11 (1.05, 1.17) **
	-	Certolizumab	1.11 (0.97, 1.28)

** = P<0.001 * = P<0.01 † = P<0.05

Table 35. BSRBR-RA cohort - Cox proportional hazard estimates of NSI comparing biologic exposure, using 'no biologic' as comparator group

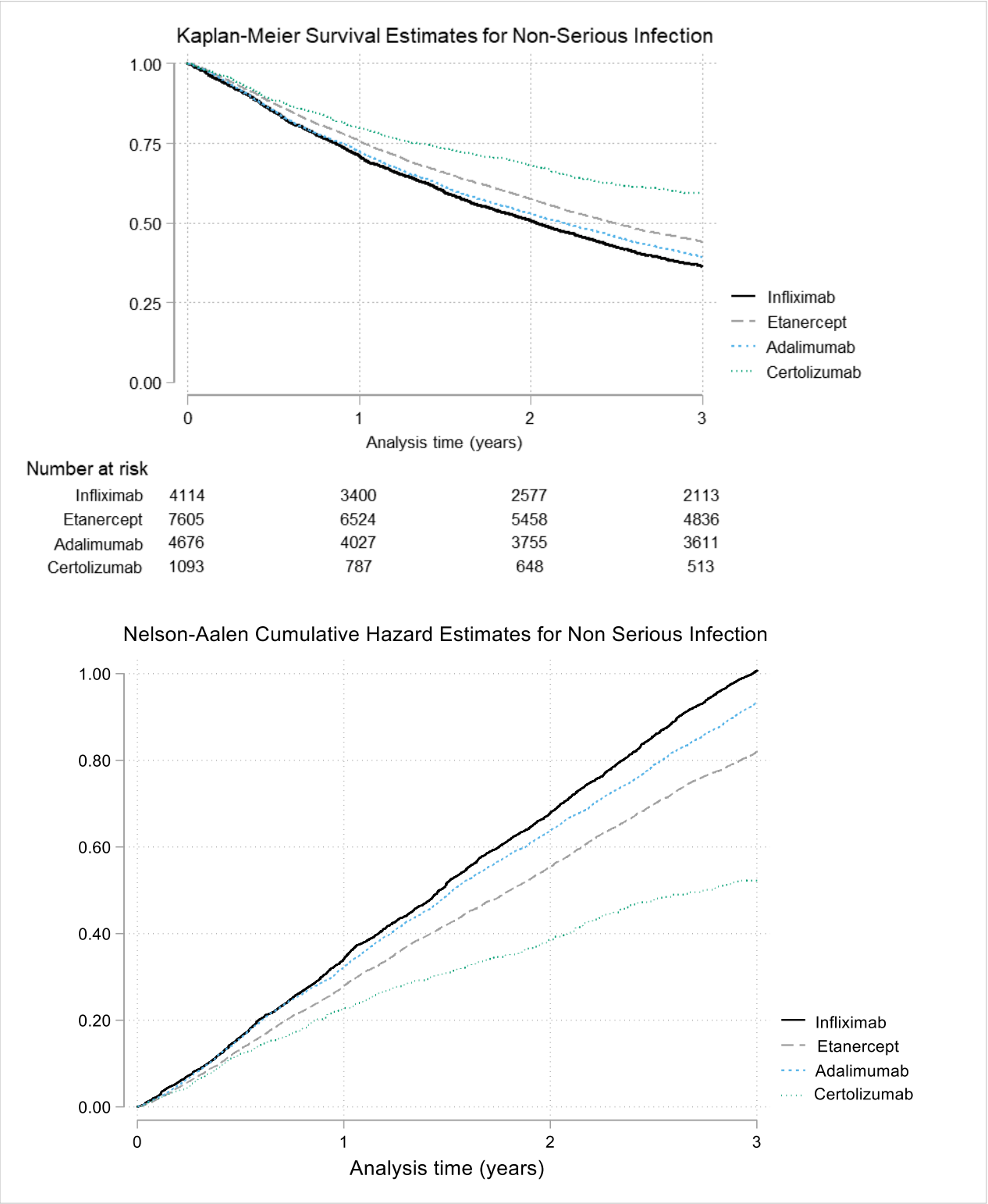
Treatment Hazard ratio (95% CI)			
Biologic exposure (ref csDMARDs only)			
Unadjusted	-	TNFi	1.52 (1.41, 1.62) **
	-	Anti-IL-6R	1.46 (1.26, 1.69) **
	-	Anti-CD20	1.74 (1.53, 1.97) **
Adjusted	-	TNFi	1.51 (1.38, 1.65) **
	-	Anti-IL-6R	1.99 (1.70, 2.34) **
	-	Anti-CD20	1.74 (1.46, 2.07) **
Imputed Adjusted	-	TNFi	1.56 (1.45, 1.68) **
	-	Anti-IL-6R	2.22 (1.94, 2.54.) **
	-	Anti-CD20	1.99 (1.76, 2.26) **

Figure 24. BSRBR-RA cohort - Kaplan-Meier and Nelson Aalen graphs for NSI with bDMARDs



These Kaplan-Meier and Nelson-Aalen graphs demonstrate the survival estimates and unadjusted cumulative hazard of non-serious infection, comparing no biologic (csDMARD cohort), TNF inhibition, IL-6 inhibition and B cell depletion. Patients receiving csDMARD demonstrates favourable survival (less NSI events) and lower cumulative hazard of NSI compared to the biologic DMARDs.

Figure 25. BSRBR-RA cohort - Kaplan-Meier and Nelson Aalen graphs for NSI with TNFi



These Kaplan-Meier and Nelson-Aalen graphs demonstrate the survival estimates and unadjusted cumulative hazard of non-serious infection, between TNFi agents (infliximab, etanercept, adalimumab and certolizumab). Patients receiving certolizumab demonstrates favourable survival (less NSI events) and lower cumulative hazard of NSI compared to the biologic other TNFi agent.

Two further analyses were performed looking at different exposure including an 'on drug time only' and an 'ever exposed' model. These analyses demonstrated comparable estimates to the primary analysis (Table 36).

A single failure competing risk survival model was performed to account for the effect of serious infection in the NSI analysis. This model did not alter any estimates (Table 37).

To account for patients who registered a second time and contributed to more than one drug cohort, standard errors were recalculated using the cluster robust sandwich estimator. This made almost no difference to the estimated confidence intervals, or p-values, and thus the interpretation appears robust (Table 38).

Table 36. BSRBR-RA cohort - Cox proportional hazard estimates of NSI comparing biologic exposure; i) primary analysis model (3-month lag-time), ii) on drug only model iii) ever exposure model (until switch).

Non serious infection Treatment Hazard ratio (95% CI)	Primary analysis (3-month lag time)	On drug only model	Ever exposure (until switch)
Unadjusted Biologics (ref TNFi):			
- Anti-IL-6R	0.96 (0.84, 1.10)	0.96 (0.84, 1.11)	1.01 (0.88, 1.16)
- Anti-CD20	1.15 (1.02, 1.29) †	1.01 (0.90, 1.14)	1.00 (0.90, 1.12)
- csDMARDs only	0.66 (0.62, 0.71) **	0.71 (0.67, 0.76) **	0.75 (0.69, 0.82) **
Adjusted Biologics (ref TNFi):			
- Anti-IL-6R	1.32 (1.15, 1.52) **	1.30 (1.13, 1.49) **	1.37 (1.20, 1.57) **
- Anti-CD20	1.15 (0.97, 1.36)	0.98 (0.81, 1.18)	1.03 (0.89, 1.19)
- csDMARDs only	0.66 (0.60, 0.72) **	0.70 (0.65, 0.76) **	0.80 (0.72, 0.91) **
Unadjusted TNFi (ref Etanercept)			
- Infliximab	1.22 (1.14, 1.31) **	1.25 (1.17, 1.34) **	1.19 (1.12, 1.27) **
- Adalimumab	1.14 (1.07, 1.22) **	1.16 (1.09, 1.24) **	1.12 (1.05, 1.19) *
- Certolizumab	0.67 (0.58, 0.78) **	0.65 (0.55, 0.77) **	0.68 (0.59, 0.80) **
Adjusted TNFi (ref Etanercept)			
- Infliximab	1.01 (0.93, 1.08)	1.01 (0.94, 1.09)	1.01 (0.94, 1.08)
- Adalimumab	1.10 (1.04, 1.16) *	1.10 (1.04, 1.17) *	1.05 (0.99, 1.12)
- Certolizumab	1.14 (0.97, 1.35)	1.13 (0.96, 1.34)	1.12 (0.96, 1.32)

Table 37. BSRBR-RA cohort - Cox proportional hazard estimates of NSI in single failure model using serious infection as competing risk

Incidence rate / 100 patient yrs (95% CI)	Incidence rate	No. infections	Follow up (Person-yrs)
Population	12.7 (12.4, 12.9)	8145	64035
Incidence rates by treatment			
- csDMARDs	8.0 (7.59, 8.47)	1260	15712
- TNFi	14.5 (14.2, 14.9)	6067	41756
- Anti-IL-6R	12.7 (11.4, 14.9)	309	2429
- Anti-CD20	13.0 (11.8, 21.3)	454	3504
Incidence rates: TNFi treatment			
- Infliximab	17.2 (16.4, 18.1)	1583	9190
- Etanercept	13.6 (13.0, 14.1)	2472	18219
- Adalimumab	14.7 (14.0, 15.4)	1764	12024
- Certolizumab	10.9 (9.6, 12.3)	246	2259

			Treatment Hazard ratio (95% CI)	
			Single failure model	Using SI as competing risk
Biologic exposure (ref TNFi)				
Unadjusted	-	Anti-IL-6R	0.87 (0.78, 0.98) †	0.88 (0.78, 0.99) † (a)
	-	Anti-CD20	0.93 (0.85, 1.02)	0.94 (0.84, 1.04)
	-	csDMARDs	0.64 (0.60, 0.68) **	0.62 (0.59, 0.66) **
Adjusted	-	Anti-IL-6R	1.32 (1.13, 1.54) **	1.40 (1.19, 1.65) ** (b)
	-	Anti-CD20	1.08 (0.96, 1.23)	1.04 (0.90, 1.20)
	-	csDMARDs	0.64 (0.60, 0.69) **	0.63 (0.58, 0.68) **
TNFi class exposure (ref Etanercept)				
Unadjusted	-	Infliximab	1.23 (1.16 1.31) **	1.32 (1.23, 1.41) ** (c)
	-	Adalimumab	1.11 (1.04, 1.18) **	1.13 (1.06, 1.21) **
	-	Certolizumab	0.77 (0.68, 0.88) **	0.74 (0.64, 0.85) **
Adjusted	-	Infliximab	1.05 (0.98, 1.13)	1.07 (1.00, 1.16) (d)
	-	Adalimumab	1.05 (0.98, 1.12)	1.06 (0.99, 1.14)
	-	Certolizumab	1.16 (0.99, 1.37)	1.14 (0.96, 1.35)

a) 237 competing SI; b) 191 competing SI; c) 137 competing SI d) 118 competing SI;

			Single failure model	Using SI as competing risk
Biologic exposure (ref csDMARDs)				
Unadjusted	-	TNFi	1.57 (1.48, 1.67) **	1.60 (1.50, 1.71) ** (a)
	-	Anti-IL-6R	1.37 (1.21, 1.55) **	1.41 (1.24, 1.61) **
	-	Anti-CD20	1.46 (1.31, 1.63) **	1.50 (1.34, 1.69) **
Adjusted	-	TNFi	1.56 (1.45, 1.67) **	1.59 (1.48, 1.72) ** (b)
	-	Anti-IL-6R	2.05 (1.78, 2.43) **	2.23 (1.87, 2.67) **
	-	Anti-CD20	1.69 (1.47, 1.94) **	1.65 (1.41, 1.93) **

a) 237 competing serious infections; b) 191 competing serious infections

This analysis has not been adjusted for time varying co-variates (cumulative NSI count, cumulative SI count and cumulative biologic use) as is a single failure model

Table 38. BSRBR-RA cohort - Cox proportional hazard estimates of NSI in multiple failure model with robust clustering to account for patients who re-registered a second time

			Treatment Hazard ratio (95% CI)	
			Primary analysis	Clustering of patients who had registered a second time
Biologic exposure (ref TNF)				
Unadjusted	-	Anti-IL-6R	0.96 (0.84, 1.10)	0.96 (0.84, 1.10)
	-	Anti-CD20	1.15 (1.02, 1.29) †	1.15 (1.02, 1.29) †
	-	csDMARDs	0.66 (0.62, 0.71) **	0.66 (0.62, 0.71) *
Adjusted	-	Anti-IL-6R	1.32 (1.15, 1.52) **	1.31 (1.14, 1.51) **
	-	Anti-CD20	1.15 (0.97, 1.36)	1.15 (0.97, 1.36)
	-	csDMARDs	0.66 (0.60, 0.72) **	0.66 (0.61, 0.72) **
TNFi class exposure (ref Etanercept)				
Unadjusted	-	Infliximab	1.22 (1.14, 1.31) **	1.22 (1.14, 1.31) **
	-	Adalimumab	1.14 (1.07, 1.22) **	1.14 (1.07, 1.22) **
	-	Certolizumab	0.67 (0.58, 0.78) **	0.67 (0.58, 0.78) **
Adjusted	-	Infliximab	1.01 (0.93, 1.08)	1.01 (0.93, 1.08)
	-	Adalimumab	1.10 (1.04, 1.16) *	1.10 (1.04, 1.16) *
	-	Certolizumab	1.14 (0.97, 1.35)	1.14 (0.97, 1.35)

7.4 Discussion

To date, non-serious infections have received little attention in the research literature, and are an under recognised component of disease burden in RA. In this large cohort I have demonstrated a high frequency of NSI affecting more than 1 in 10 patients annually. For every 100 patients there are 27 NSI events per year. This rate is comparable to that observed in other smaller observational studies (Au et al., 2011). Patients experience multiple infective episodes with respiratory infections the most frequent source.

The risk factors for developing an NSI are comparable to those observed in patients with serious infections (Doran et al., 2002b, Au et al., 2011, van Dartel et al., 2013b). This includes increasing age, comorbidity and RA disease severity. By contrast, the impact of smoking on NSI risk is distinct from what is seen with SI. Interestingly, being a current smoker is associated with a lower risk of NSI. It is possible that a smoker with an infection is less likely to be managed as an outpatient compared to a non-smoker. Indeed, cigarette smoking is a significant risk factor for severe viral and bacterial infection (Arcavi and Benowitz, 2004) and for inpatient admission when presenting with infective symptoms (Godoy et al., 2016). Smokers are susceptible to developing chronic lung disease which is also associated with increased hospitalisation, especially in the presence of infective respiratory symptoms (Strangfeld et al., 2011b, Benfield et al., 2008). It is also possible that smokers underreport their infections, perhaps attributing an NSI to a chronic cough. Lastly this may be due to reporting bias as current smokers had a lower diary return rate and we assumed that non-return meant no infection.

There was a 5% reduction in risk of NSI for each subsequent year patients were recruited to the BSRBR-RA. The rate of infections in RA patients appears to be changing over time. This has been described with

serious infective events (Ni Mhuircheartaigh et al., 2013) and likely reflects shorter RA disease duration and a lower disease burden. This could be artefactual as diary return rates have reduced in recent years.

My results demonstrate that biologics are associated with an increased risk of NSI. The csDMARD cohort had the lowest infection rates. There was a 40% decrease in risk of NSI with csDMARDs compared to TNFi. This is consistent with findings from the Corona registry, where TNFi was associated with an increased rate of outpatient infections (Au et al., 2011). It also mirrors observations from studies examining serious infection in the BSRBR-RA (Dixon et al., 2006, Galloway et al., 2011) and other observational cohorts (Lane et al., 2011, Strangfeld et al., 2011a, Askling et al., 2007a, Listing et al., 2005, Curtis et al., 2007), although the magnitude of NSI risk is far greater.

Comparisons of the risk of NSI between different biologics drugs reveals similar patterns as seen with serious infection (Rutherford et al., 2018c). Therapy with rituximab had a greater risk of infection than TNFi that did not remain statistically significant after adjustment (Rutherford et al., 2018c). This suggests that both patient and disease factors are responsible for the observed difference in NSI risk. IL-6 inhibition with tocilizumab therapy was associated with a greater risk of NSI after adjusting for both patient and disease factors.

It is biologically plausible that IL-6 inhibition would associate with infection risk. This pleomorphic cytokine has a vital role in the defence against numerous pathogens, especially bacterial and fungal, as demonstrated in primary immunodeficiency diseases involving IL-6 or its signalling pathway (Rose-John et al., 2017). Studies analysing serious infections have demonstrated an increased risk with tocilizumab compared to TNFi in the BSRBR (compared to etanercept, tocilizumab demonstrated a HR of 1.22) (Rutherford et al., 2018c) and the German biologics register (Zink et al., 2014). Whilst this finding was

not seen in a large US multi-database observational study, a greater risk of serious bacterial infection (HR 1.19) and skin and soft tissue infections (HR 2.38) was reported (Pawar et al., 2019). There is less information on NSI with tocilizumab. A high rate of NSI (40/100 patient years) was reported with tocilizumab therapy in a small German RA cohort (Lang et al., 2012). Concomitant therapy with prednisolone, leflunomide, previous exposure to rituximab and high disease activity were significant predictors of infection.

I have also demonstrated that the rates of NSI differ within the TNFi class. The highest rates were reported with infliximab and adalimumab. Compared to etanercept, adalimumab was associated with a greater risk of NSI. This differential NSI risk with the monoclonal TNFi (infliximab and adalimumab) compared to the soluble TNF receptor antagonist (etanercept) has been demonstrated previously. A meta-analysis of placebo controlled RCTs in the treatment of immune-mediated inflammatory diseases reported the lowest number of non-serious infective events with etanercept. The authors estimated a 20% higher risk with infliximab and adalimumab compared to placebo, than seen with etanercept (Dao et al., 2012b). This differential finding was also reported with herpes zoster in the German biologic registry (Strangfeld et al., 2009c) but not in the BSRBR-RA analysis (Galloway et al., 2013b).

This study has several strengths. The first is attributable to the size and quality of real-world data that the BSRBR-RA provides. There are limited missing data on baseline co-variates and accurate coding of biologics. Adverse event capture data is robust, obtained from multiple sources permitting the evaluation of non-serious events. The use of TNFi as the comparator arm rather than csDMARDs permits the comparison across biologic agents. This is more clinically relevant for physicians who are considering therapeutic options in patients who have not responded to csDMARDs. Lastly, the use of

particular statistical models has built on decades of registry analyses, learning how to handle complex datasets with time varying components and significant confounding.

We acknowledge several important limitations. We are unable to comment on the risk of NSI with certain agents as few patients were registered having received these medications. This includes golimumab and abatacept, as these cohorts were never recruited to the BSRBR-RA and the JAK inhibitors tofacitinib and baricitinib, which have only been recruited since 2017/2018. We cannot account for national guidelines, drug costs and local treatment pathways, which influence decisions on medication choice.

We describe NSI as reported to the BSRBR-RA but must acknowledge the mode of data capture for such events is inevitably incomplete and prone to misclassification bias and reporting bias. The rates of infection are likely to be underestimated but the hazards rates should be unbiased as there is no differential reporting by drug. The definitions of NSI are less robust than for SI. As we did not require a documented antibiotic prescription, a proportion of the events may not have been of infectious aetiology. Similarly, only NSI requiring antibiotics were reported by patients in their diaries and some infectious events, such as viral infections, may not have been captured at all. It is unlikely that misclassification or missed events differs significantly across the treatment groups as identical capturing mechanisms were employed, although there is still a risk of reporting bias between biologic and csDMARDs. The proportion of patients returning diaries has reduced over time which may also introduce bias; however the highest rates of NSI were seen with IL-6 inhibition, which was recruited to the BSRBR-RA in more recent years and is also the drug cohort with the lower rate of diary return. If anything, we may be underestimating the risk of NSI with IL-6 and biasing towards the null hypothesis.

Despite adjusting for baseline variables that predict NSI, there is the possibility that unmeasured confounding exists. Channelling bias is seen in observational studies where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences. Confounding by indication can be partially addressed using propensity scores. There are multiple options of statistical modelling, and we did consider a propensity model approach. However, we decided against this as it complicated our multi failure model. In our experience, results from propensity models are subtly different, and this should be considered when evaluating our results.

In conclusion, NSI events are common in patients with RA, with similar predictors to those observed with serious infections. An NSI history should be routinely captured in clinical practice. Biologics associate with a greater risk of NSI, with differences in the incidence and risk between therapies. These results provide clinicians with information on how to identify patients at greater risk of NSI and guide them on best possible drug strategies.

Chapter 8. Toxicity of JAK inhibition; systematic review and meta-analysis

This chapter investigates treatment related adverse events particularly infections, in patients receiving JAK inhibition. The first part of this chapter discusses the use of JAK inhibitors (JAKi) in RA, focussing on the efficacy of licenced agents tofacitinib and baricitinib, and those under evaluation in phase III studies, alongside their place in the management of RA. This work examines the latest research literature on the safety of these therapies and was published in *Pharmacological Research* in 2019.

The second section of this chapter examines the risk of serious infection and herpes zoster with licensed dose of JAKi, conducted by a systematic literature review and meta-analysis of phase II and III randomized controlled trials. The absolute rates of serious infection are low, with no significant increased risk compared with placebo. However across the JAKi, the incidence of herpes zoster is higher than expected for the population. The risk is numerically greatest with baricitinib although indirect comparisons between the drugs does not demonstrate any significant difference in risk. Data from post-marketing surveillance by drug registries will likely provide new insights into the differential risk of infections with JAK inhibition.

8.1 JAK inhibition in the treatment of rheumatoid arthritis

Since the end of the last century, biological therapies have taken the RA pharmaceutical market by storm. Anti-TNFs were launched in the late 1990's and have rapidly become worldwide brands. Within a decade, Humira was the highest earning product across the entire market. The success of biologics was defined by their comparable high efficacy over traditional therapeutic agents. This was primarily driven by advances in specific target selectivity. Older treatments such as methotrexate and corticosteroids are comparatively blunt tools, with a myriad of effects across the immune system and dose limiting toxicity. Treatment with biologics has led to a seismic shift in RA management with a realistic goal of LDA or disease remission.

For the scientific community, the development of biologics has been a fortuitous process. The discovery of TNF blockade has shed light on important immune aberrancies in RA, assisting in the identification and targeting of sites in the inflammatory cascade by newer biological agents. Despite their success, biological therapies have several limitations: (1) they are expensive to manufacture even after their patents expire; (2) they require administration parenterally, as proteins they would be digested if administered orally; (3) they require a cold storage chain in their supply route; (4) they are inherently immunogenic, so can trigger the development of anti-drug antibodies. As our understanding of the immune system in RA continues to expand, enticing targets for future immunotherapies have been identified. The drug development world for small molecular entities has been waiting in the wings and is now emerging into the limelight as a first line treatment option in RA. These small molecular inhibitors demonstrate equivalent or even superior efficacy to biologics and are free from many of their limitations.

8.1.1 The JAK-STAT pathway

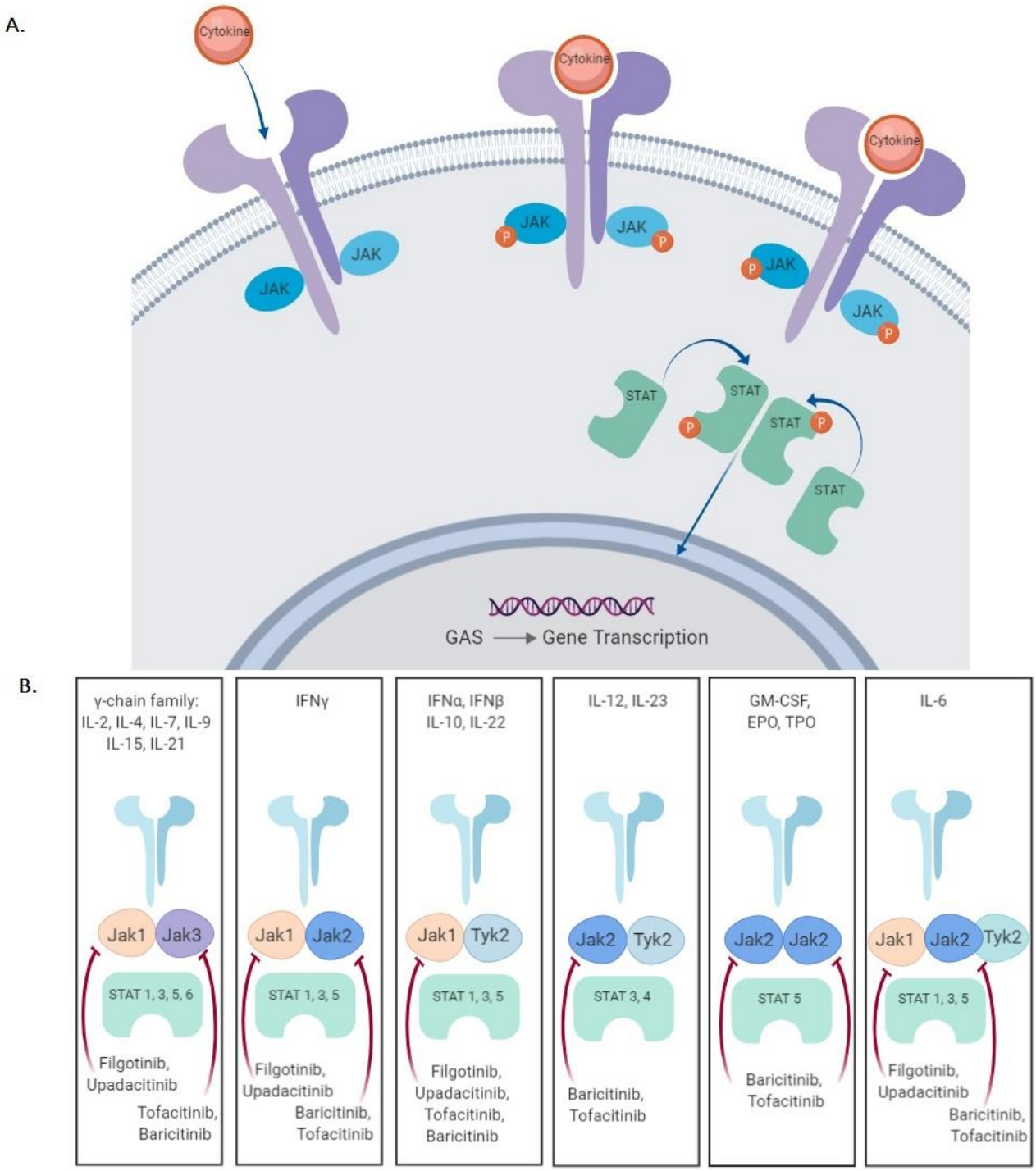
Janus kinases (JAKs) belong to the family of tyrosine kinases enzymes recognised by their ability to phosphorylate tyrosine residues, altering the function of the protein that they are contained in. They are able to transfer extracellular signals from cell surface receptors to the nucleus, changing DNA transcription and the subsequent translation of proteins. The JAK-STAT pathway operates downstream of more than 50 cytokines and growth factors and is regarded as a central communication node for the immune system (Villarino et al., 2017). There are four members of the JAK family: JAK1, JAK2, JAK3, and TYK2. Each cell surface receptor requires a pair of JAKs as either identical homodimers (e.g. JAK2/JAK2) or heterodimers (e.g. JAK1/JAK3) in order to signal (Murray, 2007). This is in turn activates STAT proteins (signal transducers and activators of transcription), which as their names suggests target gene promoters to activate transcription (Kisseleva et al., 2002). Each pair of JAKs have different activating ligands and downstream effector actions (Figure 26).

There are a number of human models for malfunctioning of the JAK-STAT pathway. The most dramatic evidence for how critical this pathway is comes from patients with severe combined immunodeficiency (SCID). This primary immunodeficiency results in recurrent severe infections and failure to thrive. A patient with SCID was identified as having a mutation in JAK3 in which a single amino acid substitution prevented JAK3–receptor interaction. This blocked a range of cytokine stimuli and severely impacted T cell, NK, and B cell development and function (Cacalano et al., 1999, O'Shea et al., 2015). Negative mutations in STAT3 result in hyperimmunoglobulin E syndrome (Job's syndrome), characterized by recurrent cutaneous and sinopulmonary bacterial infections. STAT3 mediates signalling through several classes of receptor and is essential for the production of 1L-17 and the subsequent recruitment of neutrophils, explaining the abnormalities seen with this disorder. Conversely, several

myeloproliferative diseases are driven by an activating mutations of JAK2, which is crucial for downstream signal transduction of erythropoietin and thrombopoietin (O'Shea et al., 2015).

The development of small molecules which inhibit the JAK enzymes (JAK inhibitors; JAKi) has the potential to be a game changer. These agents are beginning to demonstrate efficacy across a septum of rheumatic diseases, with results that have not been seen since the launch of TNF inhibitors. As a class they are on par if not superior to biologics in their efficacy. Additionally, they are orally administered, demonstrate a rapid onset of action and in the case of an adverse event, their short half-life allows rapid reversal of immunosuppressive effects.

Figure 26. a) The JAK-Stat signalling pathway and b) cytokine signally through JAK/Stat combination



Upon binding to a cytokine, the cytokine receptor associated JAKs become activated. These JAKs mediate phosphorylation of specific receptor tyrosine residues and recruited STATs. Activated STATs are released from the receptor, dimerize, translocate to the nucleus and bind to members of the GAS (Gamma Activated Site) family of enhancers. JAK: Janus kinase; TYK: Tyrosine kinase; STAT: Signal Transducer and Activator of Transcription; IFN: Interferon; IL: Interleukin; EPO: Erythropoietin; GM-CSF: Granulocyte/macrophage colony stimulating factor; TP0: Thrombopoietin.

8.1.2 Licensed JAK inhibition with market authorisation for the treatment of RA

There are currently two licenced small molecule JAKi in rheumatic diseases; tofacitinib and baricitinib. These agents block more than one JAK enzyme and prevent the signalling of multiple cytokines. The inhibition profiles are however dose dependent. At higher doses both tofacitinib and baricitinib can block other members of the JAK family and lead to 'pan-JAK' inhibition (Winthrop, 2017, O'Shea et al., 2013a, Clark et al., 2014).

Tofacitinib

Tofacitinib (Xeljanz®, formerly designated CP 690,550) was developed by Pfizer and became the first JAK inhibitor to be approved for the treatment of RA by the Food and Drug Administration (FDA) in 2012. The European Medicines Agency (EMA) approved tofacitinib in 2017. In the treatment of psoriatic arthritis (PsA), tofacitinib was approved by the FDA in 2017 and EMA in 2018. The FDA declined approval for psoriasis on issues of clinical efficacy and long-term safety.

Tofacitinib was originally described as a selective JAK3 inhibitor. It blocks JAK3 and JAK1, with some affinity for JAK2 and limited affinity for TYK2. (Scott, 2013). Consequently tofacitinib potently inhibits signalling of γc chain cytokines (IL-2, IL-4, IL-7, IL-15 and IL-21) via JAK3; but also blocks IFN-γ and IL-6 via JAK1-JAK2; and to a lesser extent IL-12 and IL-23 via JAK2-Tyk2 (Scott, 2013, Ghoreschi et al., 2011). Tofacitinib is metabolised and cleared by the liver (70%) and kidneys (30%). Metabolism is primarily facilitated by CYP3A4 with minor contribution from CYP2C19 (Winthrop, 2017). Exposure is decreased when co-administered with potent CYP inducers (e.g. rifampicin), whilst exposure is increased when

co-administered with potent inhibitors of CYP3A4 (e.g. ketoconazole) or CYP2C19 (e.g. fluconazole). The dose should be reduced to 5mg once daily in patients co-prescribed CYP3A4 or CYP2C19 inhibitors or in severe renal impairment (creatinine clearance <30 mL/min) ((EMA), 16/03/2017).

In RA, tofacitinib has demonstrated significant efficacy in phase II and III RCTs in adult patients, both in combination with csDMARDs including methotrexate, and as a monotherapy. Seven phase III RCTs have been conducted; ORAL Solo, Start, Sync, Step, Scan, Standard and Strategy (Table 39).

The most substantial body of real-world evidence comes from the US, where tofacitinib has been available since 2012. Results from the US Corrona RA registry reported patients initiating tofacitinib had longer disease duration and greater exposer to previous TNFi or biologic DMARDs (bDMARDs) than patients initiating a traditional bDMARD (Kavanaugh AF). There was no difference in efficacy between tofacitinib monotherapy and tofacitinib combination therapy or TNFi combination therapy in bDMARD experienced patients (Reed et al., 2016).

A retrospective cohort study of patients using data from the US Commercial Claims and Encounters database reported similar efficacy rates at 1-year between tofacitinib and non-TNF biologics (Machado et al., 2018). An observational Japanese study reported 60% of patients achieved ≥50% improvement in clinical disease activity index (CDAI), with remission rates higher in biologic-naïve patients (Mori et al., 2018).The Swiss Clinical Quality Management registry (SCQM) also reported high rates of LDA and remission (Mueller R). Crude drug retention rates were similar for tofacitinib as other biologics, with a lower risk of drug discontinuation compared to TNFi (Finckh et al., 2017).

Table 39. Tofacitinib published pivotal phase III RCTs

Phase II RCT	Cohort, duration, comparator	Outcomes
ORAL Solo (Fleischmann et al., 2012b)	- n=611, cs/bDMARD-IR - 6-months - PBO	- At 3 months; significant improvement in ACR20, ACR50, ACR70 and HAQ-DI compared to placebo. - Percentage with DAS28 <2.6 was not significantly higher than placebo
ORAL Start (Lee et al., 2014)	- n=958, MTX-naïve - 24-months - MTX	- At 6 months; significantly higher ACR70 with 5mg & 10mg doses compared to MTX (26%, 38% v 12%). - Changes in mTSS from baseline significantly smaller (although modest).
ORAL Sync (Kremer et al., 2013)	- n=792, csDMARD-IR - 12-months - PBO, with DMARD	- At 6 months; significant improvements in ACR20 & percentage with DAS28<2.6 compared to placebo - At 3 months; significant improvement in HAQ-DI
ORAL Step (Burmester et al., 2013)	- n=399, TNFi-IR - 6-months - PBO, with MTX	- At 3 months; significant improvement in ACR20, HAQ-DI & percentage with DAS28<2.6.
ORAL Scan (van der Heijde et al., 2013)	- n=797, MTX-IR - 24-months - PBO, with MTX	- At 6 months; significantly smaller changes in mTSS from baseline with 10mg dose only.
ORAL Standard (van Vollenhoven et al., 2012)	- n=717, MTX-IR - 12-months - ADA or PBO, with MTX	- At 6 months; ACR20 significantly higher with 5mg, 10mg tofacitinib, ADA v MTX (52%, 53%, 47% v 28%) - Superior to placebo, numerically similar to ADA.
ORAL Strategy (Fleischmann et al., 2017a)	- n=1146, MTX-IR - 12-months - ADA or PBO, with MTX	- At 6 months; ACR50 were 38% tofacitinib, 46% tofacitinib/MTX & 44% ADA/MTX. - Non-inferiority for tofacitinib /MTX V ADA but not tofacitinib monotherapy.

MTX = Methotrexate; PBO = Placebo; IR = Inadequately response.

Baricitinib

Baricitinib (Olumiant ®) was developed by Eli Lily and approved by the EMA in 2017. The FDA approved the 2mg dose in 2018 but declined approval of the 4mg dose citing safety concerns. Baricitinib inhibits JAK1 and JAK2, and to a much lesser extent TYK2. It is considered a JAK3 sparing agent with a 100-fold selectivity for JAK1 and JAK2 (Clark et al., 2014). In vitro studies have demonstrated that baricitinib inhibits IFN-γ and IL-6 via JAK1-JAK2, IL-12/23 via JAK2-TYK2 and erythropoietin and granulocyte-macrophage colony-stimulating factor via JAK2-JAK2 (Richez et al., 2017). Baricitinib undergoes renal excretion through glomerular filtration and active secretion. Less than 10% is metabolised, mediated by CYP3A4. Exposure is generally not affected by co-administration of CYP3A4 inducers or CYP3A4 / CYP2C19 inhibitors. A reduced dose of 2mg is recommended for patients with a creatinine clearance between 30-60mls/minute or those taking OAT3 inhibitors such as probenecid ((EMA), 31/03/2017).

In RA baricitinib has demonstrated significant efficacy in phase II and III RCTs. The development program includes one phase I, three phase II and four phase III trials: RA Begin, Build, Beam, and Beacon (Table 40). Patients completing phase III RCTs entered LTEs RA-Beyond and RA-Balance. A sub-study within RA-Beyond examined dose reduction from 4mg to 2mg in patients who achieved clinical disease control with 4mg. Dose tapering resulted in a statistically significant, if modest increase in disease activity, although most patients could retain disease control or regain it by returning to the 4mg dose (Takeuchi et al., 2018). As baricitinib has only recently been approved in the EU and US, less data are available on its use in the 'real world'. The baricitinib RCTs suggested a potential safety signal, which led to a delay in licensing in North America (only the 2mg dose is licenced). In the EU both doses are licenced for use in RA. Registry data will be crucial in further characterising safety signals.

Table 40. Baricitinib published pivotal phase III RCTs

Phase II RCT	Cohort, duration, comparator	Outcomes
RA-Begin (Fleischmann et al., 2017b)	- n=588, csDMARD-naive - 52-weeks - 4mg dose Vs PBO, with/without MTX	- At 24 weeks; ACR20 was non-inferior with baricitinib monotherapy Vs MTX (77% v 62%). Improved ACR50, ACR70, DAS28-CRP, HAQ-DI & SDAI - Significantly less radiographic progression with baricitinib /MTX versus MTX.
RA-Build (Dougados and van der Heijde, 2017)	- n=684, csDMARD-IR - 24-weeks - 2mg or 4mg Vs PBO, with csDMARD	- At 12 weeks; ACR20 significantly higher with 4mg dose versus PBO (62% v 39%). - Improved DAS28, SDAI, HAQ-DI, & radiographic progression with both doses.
RA-Beam (Taylor et al., 2017b)	- n=1307, csDMARD-IR - 52-weeks - 4mg dose Vs PBO or ADA, with DMARD	- At 12 weeks; ACR20 significantly higher with baricitinib 4mg and ADA v PBO (70%, 61% v 40%). - Non-inferior baricitinib V ADA (margin of 12%), considered superior (P=0.01). - Improved DAS28, SDAI, HAQ-DI & x-ray progression.
RA-Beacon (Smolen et al., 2016b)	- n=527, bDMARD-IR - 24-week - 2mg or 4mg Vs PBO, with csDMARD	- At 12 weeks; ACR20 significantly higher with baricitinib 4mg v PBO (55% v 27%). - Improved DAS28 & HAQ-DI, but not SDAI remission.

* Abstract only. MTX = Methotrexate; PBO = Placebo; IR = Inadequately response.

In clinical practice, JAKi are commenced after patients have failed to respond to csDMARDs such as methotrexate. However, they are often used after biologics have been trialled. This is due to clinical inertia. The JAKi are the latest drugs to come to market, and as such there are less safety data compared to biologics.

The 2017 European guidelines for the management of RA recommend the addition of a biologic or JAKi after failing to respond to the first csDMARD strategy and if poor prognostic factors are present (Smolen et al., 2017b). A small preference is given to biologics due to the availability of long-term safety data. A similar approach was previously used in justifying the use of TNFi as the preferred first-line biologic over other biologics due to a long-term efficacy and safety data from registries. The 2015 American guidelines include tofacitinib alone as the only FDA-approved JAKi (Singh et al., 2016a). If disease activity persists despite first csDMARD strategy, the guidelines recommend without preference, either the use of combination csDMARD, the addition of a biologic or the addition of tofacitinib. Hierarchy of choice is not ranked as there is no evidence of superiority from direct comparison trials. If disease activity remains high despite a biologic, a second-line biologic is recommended over tofacitinib. This is justified by longer-term safety data and clinical experience, without differences in clinical efficacy.

JAKi are efficacious in both patients who are biologic-naive and those who had failed previous biologics, although response rates are numerically greater in the biologic-naïve group (Charles-Schoeman et al., 2016, Mori et al., 2018). This contrasts with earlier biologic trial data, in which the clinical response was significantly lower when a second biologic was used after a prior failure. The improved efficacy of JAKi

in patients who have failed a biologic may relate to changes in the definition of biologic failure and a lower threshold for switching therapies. This has resulted in a population who may align more with a biologic naive cohort.

8.1.3 JAK inhibitors in development

Next-generation JAK inhibitors have been designed with a view to improve selective affinity for one or more of the four JAK enzymes. The principle aim of these agents is to reduce non-selective pan JAK inhibition in the hope that this will lessen unwanted adverse effects without a decline in clinical efficacy. These agents are yet to be licensed in Europe or North America.

Upadacitinib

Upadacitinib (ABT-494) was developed by AbbVie (Banerjee et al., 2017). It is a selective JAK1 inhibitor, with 74 and 58 -fold selectivity for JAK1 over JAK2 and JAK3 respectively (Genovese et al., 2016b). This is due to its ability to bind JAK1 at two separate sites. In vitro research suggests that JAK1 inhibition might be largely responsible for the in vivo efficacy of JAK inhibitors in immune-inflammatory diseases (Haan et al., 2011). Upadacitinib exposure is weakly decreased with strong inhibition of CYP3A4 and moderately increased with broad CYP induction (Mohamed et al., 2017). Approximately 20% is eliminated by the kidneys. (Klünder et al., 2017).

In RA, upadacitinib has been evaluated in two phase II dose ranging studies: BALANCE I (in TNF inadequate responders) and BALANCE II (in methotrexate inadequate responders), in which a significant and rapid dose-response were seen for ACR20, 50 and 70 responses (Kremer et al., 2016, Genovese et al., 2016b). Upadacitinib is currently being evaluated in six phase III RCTs, four of these are complete with published data: SELECT-Next, Beyond, Early and Monotherapy (Table 41). Two phase III RCTs are ongoing, SELECT-Compare examines upadacitinib versus adalimumab versus placebo in methotrexate inadequate responders (projected to complete in 2020) and SELECT-Choice is a non-inferiority study examining upadacitinib versus abatacept in bDMARD inadequate responders (estimated to complete in 2021)

Filgotinib

Filgotinib (GLPG0634) has been co-developed by Galapagos and Gilead Sciences (Banerjee et al., 2017). Filgotinib is also a selective JAK1 inhibitor. In whole blood assays it shows a 30-fold selectivity for JAK1 over JAK2-dependent signalling (Taylor et al., 2017a). Preclinical studies demonstrated that filgotinib forms an active metabolite that exhibits a similar JAK1 selectivity profile as filgotinib, albeit less potent. This metabolite contributes to the relatively long duration of JAK1 inhibition following filgotinib dosing (Namour et al., 2015). Neither filgotinib nor its active metabolite inhibit or induce CYP activity at clinically relevant concentrations, a potentially attractive feature for patients on multiple medications.

In RA, filgotinib has been investigated in two phase IIb studies. DARWIN-1 was a 24-week trial in MTX inadequate responders with background MTX. At week 12, ACR 20 responses were significantly higher with filgotinib 100 and 200 mg, with no difference between once-daily and twice-daily regimens. Onset

of action was rapid and dose-dependent responses were observed for most efficacy endpoints (Westhovens et al., 2017). DARWIN-2 was a 24-week trial of filgotinib monotherapy in MTX inadequate responders. At week 12, significantly more patients receiving filgotinib at any dose achieved ACR20 responses versus placebo (≥65% vs 29%). In both studies there were statistically significant improvements in ACR50, ACR70, DAS28-CRP, CDAI and HAQ-DI (Kavanaugh et al., 2016).

Filgotinib is currently being evaluated in three phase III RCTs in RA and one LTE. FINCH 1 is a 52-week RCT in MTX inadequate responders, comparing filgotinib plus MTX versus placebo and adalimumab. FINCH 2 is a 24-week RCT in DMARD inadequate responders taking csDMARDs. It completed in June 2018, although no results have been published at time of writing. FINCH 3 is a 52-week RCT in MTX-naïve patients examining filgotinib in combination with MTX, as well as monotherapy.

Possible breakthrough agents and those that have been discontinued

Peficitinib inhibits JAK1, JAK2, JAK3, and TYK2 activities with moderate selectivity for JAK3 inhibition. The efficacy of peficitinib for the treatment of RA has been investigated in phase II trials, with similar efficacy as seen with other JAKi (Takeuchi et al., 2015b, Genovese et al., 2017, Kivitz et al., 2017). PF-06651600 targets JAK3 and was developed by modifying the structure of tofacitinib to allow irreversible covalent binding and optimize selectivity. It is being evaluated in the treatment of RA (Thorarensen et al., 2017). Decernotinib is a selective JAK3 inhibitor that demonstrated comparable efficacy to tofacitinib in RA (Genovese et al., 2016c). However, it was reported to cause neutropenia and, as a potent inhibitor of CYP3A4, was likely to contribute to multiple drug interactions. As such the manufacturer decided not to proceed with development of this drug for RA (Taylor et al., 2017a).

Table 41. Upadacitinib published pivotal phase III RCTs

Phase II RCT	Cohort, duration, comparator	Outcomes
SELECT-Next (Burmester et al., 2018)	- n=661, csDMARD-IR - 12-weeks - 15mg, 30mg Vs PBO, with csDMARD	- At 12 weeks; significantly higher ACR20 (64%, 66% v 39%) & DAS28-CRP≤3.2 (48%, 48% v 17%) with 15mg, 30mg v PBO respectively - Improved HAQ-DI, FACIT & stiffness.
SELECT-Beyond (Genovese et al., 2018)	- n=498, bDMARD-IR - 12-weeks - 15mg, 30mg Vs PBO, with csDMARD	- At 12 weeks; significantly higher ACR20 (65%, 56% v 28%) & DAS28-CRP≤3.2 (43%, 42% v 14%) with 15mg, 30mg v PBO. - Improvement in ACR50 (& ACR70 with 30mg only). - At 24 weeks, responses were similar between patients on PBO to UPA at 12 weeks vs UPA from baseline.
SELECT-Early* (van Vollenhoven R, 2018)	- n=945, MTX naive - 24-weeks - 15mg, 30mg Vs MTX	- At 12 weeks; significantly higher ACR50 (52%, 56% v 28%) & DAS28-CRP≤2.6 (48%,50% v 19%) with 15mg, 30mg v PBO. - Less radiographic progression at both doses.
SELECT-Monotherapy* (Smolen et al., 2018a)	- n=648, cs/bDMARD-IR - 14-week - 15mg, 30mg Vs PBO,	- At 14 weeks; significantly higher ACR20 (68%, 71% v 41%) & DAS28-CRP≤3.2 (45%,53% v 19%) with 15mg, 30mg v PBO. - Improved ACR50, ACR70 & DAS28<2.6.

* Abstract only. UPA = Upadacitinib. PBO = Placebo; IR = Inadequately response.

8.1.4 Safety of JAK inhibitors

The more recent focus on small molecule inhibitors after years of biological therapy requires careful consideration of their safety. Unlike biologics, JAKi's demonstrate a dose-proportional pharmacokinetic profile. At higher doses they exhibit 'pan-JAK' inhibition with resultant off target effects (O'Shea et al., 2013a). The therapeutic window is controlled by hepatic metabolism facilitated by cytochrome P450 and renal clearance through glomerular filtration and active secretion. This introduces the risk of toxicity when co-administered with potent CYP3A4 (e.g., ketoconazole) or CYP2C19 inhibitors (e.g. fluconazole) or in patients with severe renal impairment. Current recommendations advise dose reduction in such circumstances ((EMA), 16/03/2017, (EMA), 31/03/2017). It is clear that further work is required to fully characterize the safety profile of JAKi. Registry data will play a prominent role, assessing safety and efficacy in a more heterogenous population. Prescribing clinicians should be vigilant and keep an open mind regarding novel adverse events.

Infection

As JAK inhibition results in the suppression of multiple integral elements of the immune response, infection represents a major concern (Winthrop, 2017). The introduction of JAKi was initially overshadowed by concerns of opportunistic infection observed at higher doses. As the phase III trials have emerged and LTE data have been evaluated, the absolute risk of serious adverse events appears comparable to biologics.

Pooled data from tofacitinib studies with 19,406 patient years demonstrated a serious infection incidence rate of 2.7 per 100 patient years (Cohen et al., 2017). Glucocorticoids, baseline lymphopenia, line of therapy (3rd line vs 2nd) and geographical region (Asia, Europe, and Latin America versus USA and Canada) are associated with greater risk (Cohen et al., 2017). Similar rates of serious infection were reported with baricitinib. A pooled analysis including 6637 patient years reported an incidence rate of 2.9 per 100 patient years (Smolen et al., 2018b). The risk of serious infections is comparable to published rates for biologics. A meta-analysis reported a rate of 3.02 and 2.50 in tofacitinib RCTs and LTEs, which was similar to rates seen with biologics (range 3.04 to 5.45) (Strand et al., 2015c).

The most recognized infectious complication with JAKi has been the reactivation of varicella zoster virus, with incidence rates of 4.4 per 100 patient-years with tofacitinib (Winthrop et al., 2014) and 3.2 with baricitinib (Smolen et al., 2018b). These rates are substantially higher in Asia (7.7 with tofacitinib) (Winthrop et al., 2014). An observational analysis using US health plan data reported an approximate doubling in the rate of herpes zoster with tofacitinib compared to biologics (adjusted hazard rate 2.01 compared to abatacept) (Curtis et al., 2016b). The highest rates are seen in older patients with co-prescription of glucocorticoids or MTX, and in those from Japan or Korea (Winthrop et al., 2014). There are very few cases of multi-dermatomal or disseminated herpes, and no cases of visceral disease or death (Winthrop et al., 2014).

Tuberculosis was reported with both tofacitinib and baricitinib. With tofacitinib there were 26 cases identified from RCTs and LTEs, of which 20 occurred with the 10mg dose, and all but two cases had negative screening at trial entry (Smolen et al., 2016a). With baricitinib there were 10 cases, all of which occurred in endemic areas (Smolen et al., 2018b). Screening for tuberculosis (i.e. with Interferon Gamma Release Assay, IGRA) is recommended across the JAK class.

Malignancy

A theoretical concern exists regarding the risk of malignancy. JAKi's block interferon signaling, a central coordinator in tumour surveillance, and NK cells known for their ability to kill tumour cells (Dunn et al., 2006). This cancer signal may have a longer latency than observed with other safety outcomes. Pooled data from tofacitinib studies with 19,406 patient years recorded 173 malignancies and 118 non-melanoma skin cancers (NMSC) in 6194 patients (Cohen et al., 2017). The most common cancers were lung (n=32) followed by breast (n=25) and lymphoproliferative (n=19) (Cohen et al., 2017). The standardized incidence ratios for all malignancies and for NMSC were within the expected range seen in patients with moderate-to-severe RA, and the rate remained stable over time. (Curtis et al., 2016a). Fewer data are available for baricitinib. A safety analysis of eight RCTs and one ongoing LTE study with 6637 patient years recorded 52 malignancies and 24 NMSC in 3492 patients (46% had exposure data for less than two years). Although reassuring, long term experience with these agents are limited in comparison to biologics such as TNF inhibitors. Post-marketing surveillance (e.g. drug registries) is essential in evaluating the risk of malignancy with JAKi (Winthrop, 2017).

Venous thromboembolism (VTE)

Analysis of VTE across tofacitinib studies in RA, psoriasis, PsA and ulcerative colitis showed no evidence of an increased risk (Mease, 2017). At three months follow up there were two VTEs in the placebo arm and none in the treatment arms. In total there were three deep vein thromboses (two in RA, and one in PsA) and five pulmonary emboli (PE) (all in RA). In general, the numbers of VTEs were small, with a

surprising higher rate of PE than DVT, which may suggest underreporting of DVTs. The incidence rates for PE in the RA RCTs were similar to those reported with biologics (Mease, 2017).

The baricitinib studies identified an imbalance in the number of VTEs. An analysis of pooled data in 3492 baricitinib-RA treated patients recorded 31 VTEs. At six months follow up, six patients taking with baricitinib 4mg had a VTE. There were no VTEs in the placebo arm. All patients with VTE had multiple risk factors and the rates remained stable over time. At longer exposure, the overall incidence rate for DVT/PE was 0.5 per 100 patient years. The rate was comparable between doses (0.5 vs 0.6 in 2mg and 4mg respectively) (Weinblatt M, 2017, Smolen et al., 2018b). The published incidence rate for DVT/PE in the RA population is 0.3 to 0.8 per 100 patient years (Ogdie et al., 2017). The potential signal around VTE that have been observed in the data is unconvincing at present. Clinically, it would be wise to be cautious in patients with risks factors for VTE, and to consider other therapies first. However, it would be wrong to suggest that there is conclusive evidence of a VTE risk with baricitinib therapy.

Lipids

Hypercholesterolemia and changes in lipoprotein composition have been observed with JAK inhibitors. It remains unclear if or how inhibition of the JAK pathway influences lipid structure and function. There are similarities to the lipid raising effects seen with the IL-6 inhibitor tocilizumab, suggesting the mechanism may lie in blockade of the IL-6 pathway. Invitro studies have demonstrated that tofacitinib reduces cholesterol ester catabolism (Charles-Schoeman et al., 2015) and increases lipid release from macrophages through its actions on reverse cholesterol transport (Perez-Baos et al., 2017).

In tofacitinib RA studies a 16–30% dose-dependent increase in HDL and LDL has been reported (McInnes et al., 2014). Levels increased within one month and then plateaued. A dose-dependent increase in HDL, LDL and triglycerides was also observed with baricitinib. Despite these changes the LDL:HDL ratio remained stable. With both agents, alterations in lipids correlated with improvements in RA disease activity (Kremer et al., 2017). Patients with RA demonstrate abnormal lipids profiles as a direct consequence of their disease. It is postulated that JAKi restore lipid balance. However, this seem unlikely as data from ulcerative colitis trials, where there is no established link with lipid metabolism, report unfavourable changes in lipid profiles with JAKi. Although elevations in LDL levels is concerning, this did not translate into increased cardiovascular events during the RCTs or LTEs. It is important that we don't assume that the elevation in lipids can be ignored. Patients who demonstrated changes were treated with statins, with LDL levels reversing in response to therapy (Taylor et al., 2018). It may be more appropriate to conclude that in patients receiving JAKi, who are treated for hypercholesteremia, there is no added increase in cardiovascular risk. Longer-term data are available with tocilizumab, which reassuringly has not demonstrated an associated risk of cardiovascular disease (Xie et al., 2018).

Gastrointestinal Perforation

An elevated incidence of lower intestinal perforations has been reported with JAKi, similar to that seen with tocilizumab (Strangfeld et al., 2016). There were 22 GI perforations from the tofacitinib pooled data with 19 406-person years of drug exposure, with an incidence rate of 0.11 per 100 patient years (Cohen et al., 2017). A study using health plan data reported a two-fold risk of GI perforation among tofacitinib users compared to those receiving TNFi, although this was not statistically significant (Xie et al., 2016). A baricitinib safety analysis with 6637-patient years reported three GI perforations, with an incidence rate of 0.05 per 100 patient years (Genovese, 2017). As seen with tocilizumab the risk was greatest in patients with known diverticular disease. Data from tocilizumab studies have highlighted

that patients present atypically with subtle clinical signs and a blunted inflammatory response (Strangfeld et al., 2017a). It would be prudent to follow similar caution with patients receiving JAKi.

Pregnancy

Small molecule JAKi potentially cross the placenta. Due to the unknown risks to mother and child, RCTs excluded pregnant patients and required the use of effective contraception by all women of child-bearing potential. Nonetheless pregnancies did occur and outcomes recorded where possible. Of the 9815 patients enrolled in the tofacitinib RCTs, 47 pregnancies (31 with RA and 16 with psoriasis) were reported. There were 25 healthy new-borns, no foetal deaths, seven spontaneous abortions, eight medical terminations and one congenital malformation. The frequency of abortions and congenital malformation were consistent with the background population risk (Clowse et al., 2016). Despite these reassuring data, JAKi are not licensed for use in pregnancy.

In summary, the past decade has witnessed an explosion in trial data on JAKi. These drugs have the potential to be a game changer in the management of rheumatic diseases. They are advantageous in their oral availability and rapid onset of action. The efficacy demonstrated by first generation agents is on par with existing biologics, whilst emerging data with next-generation JAKi may suggest even greater success. These drugs have important dose-proportional pharmacokinetic profiles and key safety signals e.g. viral infection (shingles) which will need careful management in clinical practice. As our understanding of the implications of JAK selectivity grows, we move one step closer towards the world of personalised medicine. It is evident that JAKi are revolutionising the therapeutic armamentarium in

inflammatory driven pathologies. Clinicians must now consider the place of these drugs in the management of rheumatic disease as they appear destined to take centre stage.

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8.2 Systematic review and meta-analysis of infection risk with JAK inhibitors in RA

8.2.1 Introduction

Biological therapies have revolutionized the treatment of RA with targeted suppression of key inflammatory factors that underpin the disease pathogenesis. Their high selectivity and therapeutic efficacy have resulted in an achievable goal of clinical remission. However not all patients respond to treatment. The cytokine network in RA is complex and targeting a single cytokine does not exclusively terminate the disease. Furthermore biologics are antibodies or fusion proteins that are susceptible to immunogenicity which may result in a loss of efficacy over time (Strand et al., 2017).

Advances in our understanding of signal transduction pathways has resulted in the development of small-molecule inhibitors. These drugs target intracellular cytokine pathways and represent an attractive pharmacological alternative to biologics. The JAK-STAT pathway operates downstream of more than 50 cytokines and growth factors and it is regarded as a central communication node for the immune system (Villarino et al., 2017, O'Shea et al., 2013b). Four JAKs exist: JAK1, JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2. It is the specific combination of JAKs and STATs that determine functional outcomes of cytokine receptor stimulation.

For the treatment of RA there are currently two licenced small molecule inhibitors which target the JAK-STAT pathway. Tofacitinib inhibits JAK1, JAK3 and to a lesser extent JAK2. Tofacitinib was approved for use in RA by the FDA in 2012. The EMA did not approve tofacitinib until 2017 due to safety concerns including serious infection ((EMA), 2013). Baricitinib inhibits JAK1 and JAK2 and was approved by the EMA in 2017. The FDA approved the 2mg dose, declining approval of the 4mg dose after citing safety concerns (Nair et al., 2018). Tofacitinib and baricitinib have been incorporated into national and international RA guidelines (Singh et al., 2016b, Smolen et al., 2017a). Next-generation JAK inhibitors have been designed with a view to improved selective affinity for one or more of the four JAK enzymes. Upadacitinib is a selective JAK1 inhibitor and is being evaluated in 6 phase III trials, 2 of which have been published. At the time of writing, upadacitinib was not licensed for the treatment of RA. Filgotinib, a selective JAK1 inhibitor; decernotinib, a selective JAK3 inhibitor; and peficitinib, a pan-JAK inhibitor are under evaluation in phase III trials which have not yet been published.

The development programmes for these JAKi have identified an infection signal when compared with placebo. A safety profile is emerging with viral opportunistic infections the most characteristic infectious complication, specifically the reactivation of varicella zoster virus (VZV) leading to herpes zoster (HZ), also known as shingles (Winthrop et al., 2014). This signal may be a 'class effect' as VZV reactivation has been reported with all JAKi. How JAKi increase the risk of HZ reactivation is unclear (Ghoreschi et al., 2009, Abendroth and Arvin, 2001). The role of the different JAKs in the immune response may suggest differences in safety profiles between drugs, underpinned by their differential JAK selectivity profiles. This has important clinical implications.

I undertook a systematic review and meta-analysis to evaluate serious infections (SI) and opportunistic indicator infections including HZ in RA phase II and III clinic trials with JAKi.

8.2.2 Methods

The study was conducted in accordance with the preferred reporting items for systematic reviews guidelines (Moher et al., 2015a) and registered with the international prospective register of systematic reviews (Prospero 2017 CRD42017078791).

Search strategy and information sources

The literature was searched systematically by two investigators (K.B. and S.S.) using MEDLINE, EMBASE and Cochrane Controlled Trials Register databases. The JAKi of interest were tofacitinib, baricitinib, upadacitinib, filgotinib, decernotinib and peficitinib. The search terms were 'rheumatoid arthritis' and 'tofacitinib' 'CP-690,550', 'baricitinib', 'LY3009104', 'upadacitinib, 'ABT-494', 'filgotinib', 'GLPG0634', 'decernotinib', 'VX-509' and 'peficitinib', 'ASP015K'. The search was undertaken in September 2017 and re-run prior to the final analysis to identify further studies that could be retrieved for incorporation in the systematic review.

Study selection and data collection

I identified English language publications of phase II and III randomised control trials (RCTs). Conference abstracts were excluded. Phase II studies on JAKi were excluded if there were no phase III RCTs published. RCTs were included if they met the following criteria: (1) the study included patients diagnosed with RA based on the American College of Rheumatology criteria for RA, (2) the study evaluated tofacitinib 5mg bid, baricitinib 4mg od or upadacitinib 15mg od or equivalent (6mg bid); and

(3) the study included a placebo comparator. Studies presenting duplicate data or no safety data were excluded. No restrictions were applied to the length of follow-up. Titles and abstracts of studies retrieved using the search strategy detailed above were screened independently by two investigators, K.B. and S.S. The full text of the potential studies for inclusion were retrieved and assessed for eligibility. Study quality and risk of bias were assessed using the Cochrane Collaboration's tool (Higgins et al., 2011b).

The primary outcome of interest was SI, as defined in each study as any event associated with death, admission to hospital, or use of intravenous antibiotics. Secondary outcomes of interest included the number of opportunistic infections (OI) including rates of HZ. OI were identified from summary data, and categorised as 'indicator' infections from the proposed consensus definition of specific pathogens, or presentations of pathogens that 'indicate' the likelihood of an alteration in host immunity in the setting of biologic therapy (Winthrop et al., 2015b). This approach has been adopted previously for comparisons of infection risk between biologic therapies (Rutherford et al., 2018a, Morel et al., 2017).

Data were extracted independently. Disagreements over study eligibility or risk of bias were resolved through discussion with a third reviewer (J.G.). Data collated included the source (author, journal and publication date), study design (e.g. early escape arms), patient demographics (age, disease duration, and disease activity), anti-rheumatic drug and steroid exposure and infection event rates.

Data synthesis and statistical analysis

Analyses were undertaken using Stata 15. Infections were attributed to either drug or placebo based on the treatment exposure at the time of the event. Patient exposure years were calculated for placebo and treatment arms. Two separate analyses were undertaken. Firstly, a per protocol analysis where

patients could contribute time to both the unexposed and exposed groups, (initially to the unexposed group when receiving placebo, and thereafter to the exposed group when crossed into the treatment arm to receive the study drug). Secondly, a limited analysis in which exposure time concluded at the point unexposed patients were crossed over into the treatment arm. The per protocol analysis allows the accrual of greater exposure time to the study drug but results in comparatively shorter unexposed time and may contribute to right censoring.

Crude incidence (IR) of SI and HZ were calculated for each RCT. Relative risk between JAKi and placebo was estimated and expressed as incidence rate ratios (IRR) with 95% confidence intervals. Analysis was performed using the random-effects Mantel-Haenszel method and compared graphically with forest plots. Summary data rather than individual level data were aggregated for quantitative analyses. Network meta-analysis (NMA) was employed to allow indirect comparisons between the three JAKi. Since no head-to-head studies have been undertaken, each agent was compared directly with placebo, so the relative effectiveness of one JAK versus another was estimated indirectly, along with the level of uncertainty in this estimate. Each drug was ranked based on estimated probabilities using the parameters derived from the NMA. These were summarised by calculating the surface under the cumulative ranking curve (SUCRAs). Publication bias was assessed using funnel plots.

8.2.3 Results

Search results and trial characteristics

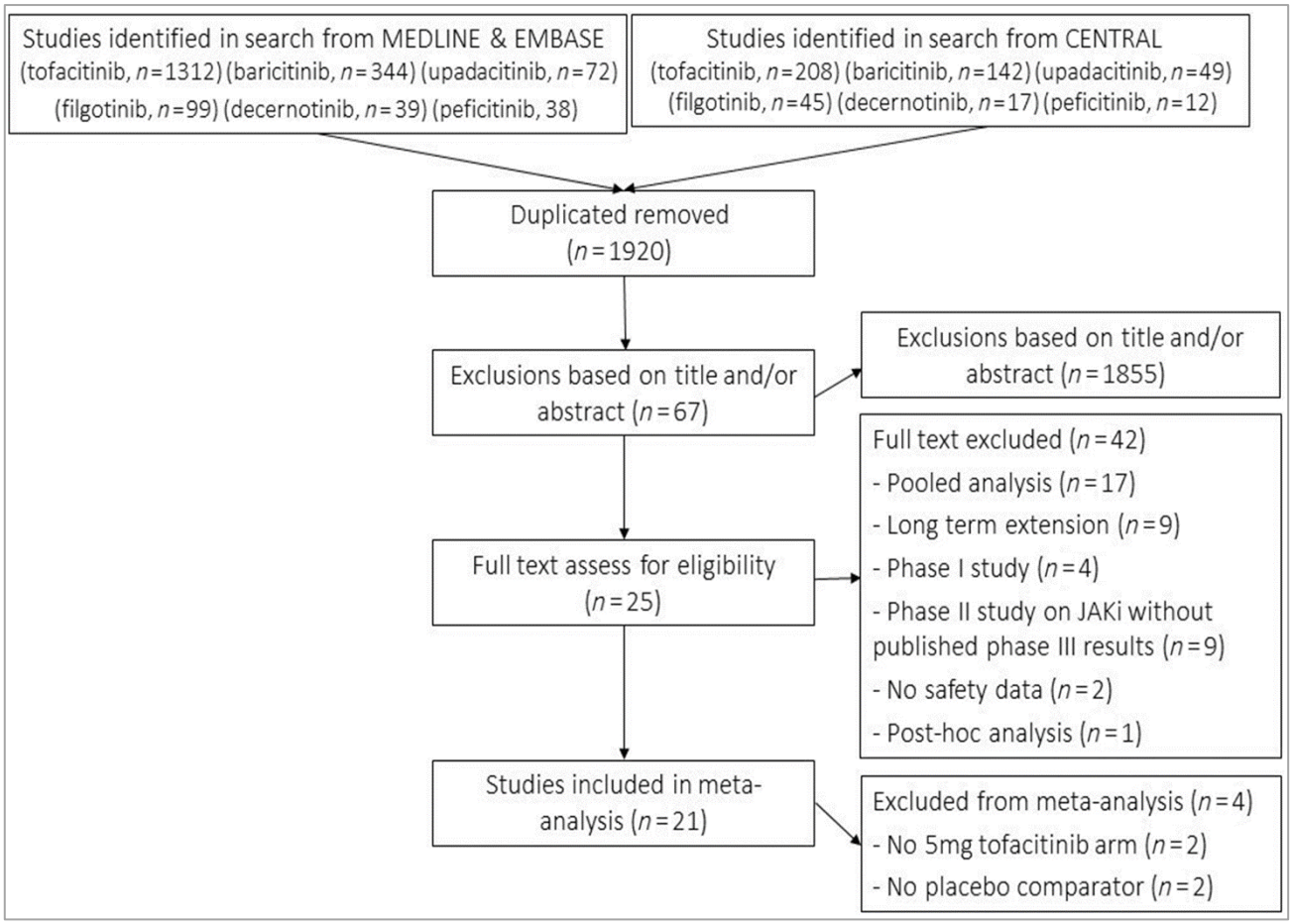
The search identified 1920 articles of which 25 were eligible phase II or III RCTs (Figure 27). Phase II studies for filgotinib, decernotinib and peficitinib were excluded as there were no published phase III

trials in RA for each of these drugs. A further 4 studies were excluded based on the treatment arm not evaluating the current licence dose of the drug or a lack of a placebo comparator. Upadacitinib is not licenced at present; a 15mg dose was chosen in anticipation of the future licensing dosage. In total, 21 studies were eligible for inclusion in our analysis; 11 tofacitinib (5888 patients), 6 baricitinib (3520 patients) and 4 upadacitinib (1736 patients) (Table 42).

Assessment of study validity revealed few sources of bias. All studies reported randomisation and blinding of participants and clinical assessors. Half did not describe methods of allocations concealment. Three studies did not account for incomplete outcome data (Table 43). Half of the studies employed an escape design which involved advancing non-responder placebo-treated patients into the active treatment arm after a predefined period treatment.

Trials included in this meta-analysis were relatively homogeneous in the patient population. The majority included patients with an inadequate response to DMARDs. Four tofacitinib, 1 baricitinib and 2 upadacitinib studies included patients with high disease activity despite biologics. Only 1 study for both tofacitinib and baricitinib included patients with early RA who were methotrexate naïve. Patients were distributed globally. Sixteen-studies recruited patient from Asia, including 3 Japanese bridging studies. Six of the 11 tofacitinib trials and all of the baricitinib and upadacitinib trials recruited patients on background stable doses of methotrexate. The majority of the studies reported on steroid therapy, and across these the exposure was comparable.

Figure 27. Flow chart of studies included in the systematic review and meta-analysis



This flow chart demonstrates the studies included in the systematic review and meta-analysis. The search identified 1920 articles of which 25 were eligible phase II or III RCTs. A further 4 studies were excluded based on the treatment arm not evaluating the current licence dose of the drug or a lack of a placebo comparator.

Table 42. Characteristics of the studies included in the systematic review and meta-analysis

Author; Study; Year	Phase study, Country	IR status (failed to respond)	Dosage and schedule (mg) + placebo	Duration of treatment; follow up	Number of Subjects JAKi; placebo	Age, years (mean ± SD)	RA duration years (range)	DAS-28 (mean ± SD)	Pred. (%)
Tofacitinib (5mg BID dose)									
(Kremer et al., 2009)	IIb. NA, LA, EU	DMARD biologic	5, 15, 30.	6 weeks	N=61 N=65	47.9 ±11 51.3 ±12	10.2 (1-35) 8.7 (1-27)	6.2** 6.0**	63.9 61.5
(Tanaka et al., 2011)	IIb. Japan	MTX	1, 3, 5, 10 + MTX.	12 weeks	N=27 N=28	50± 9.8 51±12.4	8.3 (1-26) 8.4 (1-24)	6.0 5.9	55.6 71.4
(Kremer et al., 2012)	IIb. NA, LA, EU	MTX	1, 3, 5, 10, 15, 20; + MTX.	24 weeks (NR PBO advanced at 12w)	N=71 N=69	52 ±12.8 53 ±13.4	9.0 (1-46) 9.2 (1-39)	6.1 6.1	57.7 44.9
(Fleischmann et al., 2012a)	IIb. NA, LA, EU Korea	DMARD	1,3, 5, 10, 15; or ADA.	24 weeks (NR PBO advanced at 12w)	N=49 N=59	54±13.5 53 ±13.7	8.1 (0.5-38) 10.8 (1-44)	6.6 6.6	55.15 7.6
ORAL-Solo. (Fleischmann et al., 2012b)	III. Global	DMARD biologic	5, 10.	24 weeks (All PBO advanced at 12w)	N=243 N=122	52.2 ±12 49.7 ±12	8 (0-42) 7.7 (0-28)	6.71 6.65	57.4 63.1
ORAL-Standard. (van Vollenhoven et al., 2012)	III. Global	MTX	5, 10 or ADA; + MTX.	52 weeks (NR PBO advanced at 12w, all PBO advanced at 24w)	N=204 N=108	53.0±12 [1]55.5±14 [2]51.9±14	7.6 [1]6.9 [2]9.0	6.6 [1]6.6 [2]6.3	61.8 [1]73.2 [2]59.6
ORAL-Step. (Burmester et al., 2013)	III. NA, LA, EU	TNFi MTX	5, 10; + MTX.	24 weeks; (All PBO advanced at 12w)	N=133 N=132	55.4 ±12 54.4±11.	13 (1-55) 11.3 (0-47)	6.5±1.1 6.4±1.1	63.9 62.9
ORAL-Sync. (Kremer et al., 2013)	III. Global	DMARD biologic	5, 10; + MTX.	52 weeks (NR PBO advanced at 12w, all PBO advanced at 24w)	N=315 N=159	52.7 ±12 [1]50.8±11 [2]53.3±11	8.1 (0.2-40) [1] 9.5 (0-39) [2]10.2 (0-49)	6.27±1 [1]6.44±1 [2]6.14±1	61.9 [1]59.5 [2]58.8
ORAL-Scan. (van der Heijde et al., 2013)	III. Global	MTX	5, 10; + MTX.	52 weeks (NR PBO advanced at 12w, all PBO advanced at 24w)	N=321 N=160	53.7 ±12; [1]53.2±12 [2]52.1 ±12	8.9 (0-43) [1] 8.8 (1-31) [2] 9.5 (0-44)	6.34 [1]6.25 [2]6.29	-
ORAL-Start (Lee et al., 2014)	III. Global	MTX naive	5, 10; or MTX.	24 months	N=373 N=186	50.3 48.8	2.9 2.7	6.6 6.6	Nil
(Tanaka et al., 2015)	II. Japan	DMARD	1, 3, 5, 10, 15.	12 weeks	N=52 N=52	52.6 ±11 53.3 ±11	11.0 (0-34) 6.4 (1-38)	6.41±1 5.83±1	-

Baricitinib (4mg OD dose)									
(Keystone et al., 2015)	IIb. NA, CA, EU India	MTX	1, 2, 4, 8; + MTX.	24 weeks (All PBO advanced at 12w)	N=52 N=98	53 ±10 49 ±12	5.3 (4.5)* 5.4 (4.3)*	6.0±0.9 6.3±0.8	38 52
(Tanaka et al., 2016)	II. Japan	MTX	1, 2, 4, 8; + MTX / DMARD.	12 weeks (All PBO advanced at 12w)	N=24 N=49	58 ±10 51±12.0	5.9 (4.0)* 5.1 (4.0)*	5.77±0.7 5.53±1.0	75 59
RA-Beacon (Genovese et al., 2016a)	III. Global	Biologic	2, 4; + MTX / DMARD.	24 weeks (NR PBO advanced at 16w)	N=177 N=176	56 ±11 56 ±11	14 (9)* 14 (10)*	6.6±1.1 6.6±0.9	-
RA-Beam. (Taylor et al., 2017b)	III. Global	MTX	4 or ADA; + MTX.	52 weeks (NR PBO advanced at 16w, All PBO advanced at 12w)	N=487 N=488	54 ±2 53 ±2	10 (9)* 10 (9)*	6.5±0.9 6.4±1.0	56 59
RA-Begin (Fleischmann et al., 2017b)	III. Global	MTX naive	4^1 or 4 +MTX^2	52 weeks (NR PBO advanced at 24w)	N^1=159 N^2=215 N= 210	^{1}51 ±13 ^{2}49 ±14 51 ±13	^{1}1.9 (4.7)* ^{2}1.3 (2.7)* 1.3 (4.0)*	^{1}6.6±1 ^{2}6.6 ±1 6.6±1	^{1}30 ^{2}39 36
RA-Build. (Dougados and van der Heijde, 2017)	III. Global	DMARD	2, 4; + MTX / DMARD.	24 weeks (NR PBO advanced at 16w)	N=227 N=228	52 ±12 51 ±13	8 (8)* 7 (8)*	6.2±0.9 6.2±1.0	-
Upadacitinib (6mg BID or 15mg OD dose)									
(Genovese et al., 2016b)	IIb. Global	MTX	3, 6, 12, 18 bid, 24 od; + MTX.	12 weeks	N=50 N=50	55 ±12; 55 ±12	7.0 (5.5)* 5.9 (5.3)*	5.8±1** 5.6±1**	32 16
(Kremer et al., 2016)	IIb. Global	TNF	3, 6, 12, 18 bid; + MTX / DMARD.	12 weeks	N=55 N=56	56 ±12 58 ±13	12.3 (10.6)* 12.1 (9.0)*	5.9±1** 5.8±1**	-
SELECT-Beyond (Genovese et al., 2018)	III. Global	Biologic	15, 30 od; + MTX / DMARD.	24 weeks (All PBO advanced at 24w)	N=164 N=169	56±11 58 ±11	12·4 (9.4))* 14.5 (9.2)*	5.9±1** 5.8±1**	51 44
SELECT-Next (Burmester et al., 2018)	III. Global	DMARD	15, 30 od; + MTX / DMARD.	12 weeks	N=221 N=221	53±12 56 ±12	7·3 (7·9)* 7·2 (7·5)*	5.7±1** 5.6±1**	43 48

IR = inadequate response; PBO = placebo. Disease duration = median + range

*= disease duration SD. ** = DAS28-CRP

1,2 = denote data from two placebo groups in van Vollenhoven 2012, Kremer 2013 & van der Heijde 2013 studies.

1,2 = denote data from two treatment arms (baricitinib monotherapy and baricitinib combination) in Fleischmann 2017 study.

Table 43 Cochrane risk of bias assessment for included studies in the systematic review

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias)	Blinding outcome assessment (detection bias)	Incomplete outcome date (attrition bias)	Selective reporting (reporting bias)
Tofacitinib						
Burmester et al (ORAL-Step), 2013	+	+	+	+	?	+
Fleischmann et al, 2012	+	?	+	+	+	+
Fleischmann et al (ORAL-Solo), 2012	+	+	+	+	+	+
Kremer et al, 2009	+	?	+	+	?	+
Kremer et al, 2012	+	?	+	+	+	+
Kremer et al (ORAL-Sync), 2013	+	?	+	+	+	+
Lee et al (ORAL-Start), 2014	+	+	+	+	+	+
Tanaka et al, 2011	+	?	+	+	+	+
Tanaka et al, 2015	+	+	+	+	+	+
van der Heijde et al (ORAL-Scan), 2013	+	+	+	+	+	+
van Vollenhoven et al (ORAL-Standard), 2012	+	+	+	+	+	+
Baricitinib						
Dougados et al (RA-Build), 2017	+	?	+	+	+	+
Fleischmann et al (RA-Begin), 2017	+	?	+	+	+	+
Genovese et al (RA-Beacon), 2016	+	?	+	+	+	+
Keystone et al, 2015	+	?	+	+	+	+
Tanaka et al, 2016	+	+	+	+	?	+
Taylor et al (RA-Beam), 2017	+	?	+	+	+	+
Upadacitinib						
Burmester et al (SELECT-Next), 2018	+	+	+	+	+	+
Genovese et al, 2016	+	+	+	+	+	+
Genovese et al (SELECT-Beyond), 2018	+	+	+	+	+	+
Kremer et al, 2016	+	+	+	+	+	+

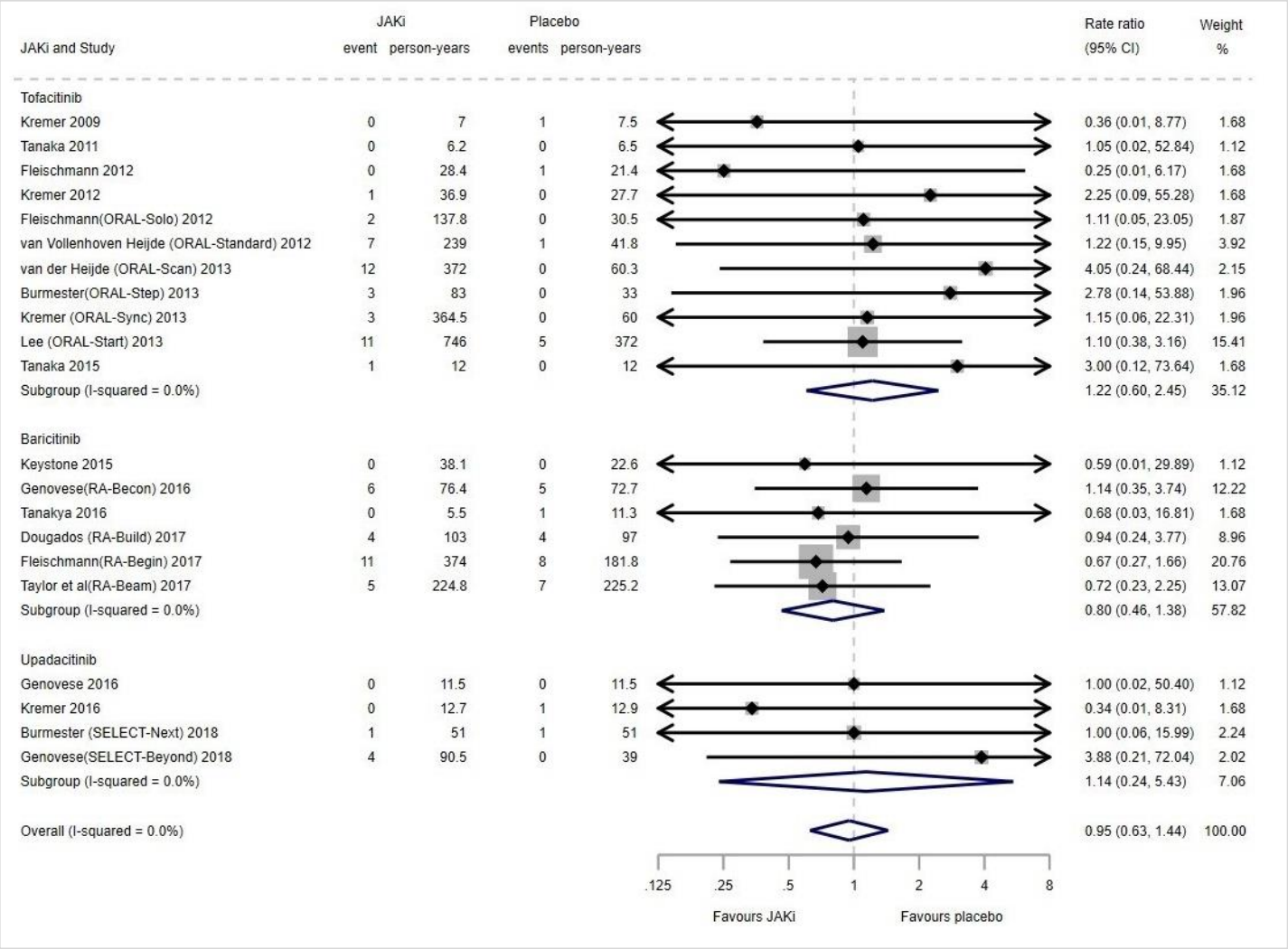
Incidence rates (IR) and incidence risk ratio (IRR) for serious infection (SI)

In the per protocol analysis, SI were reported in 40 patients receiving 5mg BID tofacitinib with 2032 patient exposure years (PEY), 26 patients receiving 4mg baricitinib with 822 PEY and 5 patients receiving 15mg or near equivalent upadacitinib with 166 PEY. Estimates of crude IR per 100 patient-years (95 % CIs) were 1.97 [CI 95% 1.41, 2.68] for tofacitinib, 3.16 [2.07, 4.63] for baricitinib and 3.02 [0.98, 7.04] for upadacitinib. In the pooled placebo group, estimates of IR were 2.50 [1.74, 3.48] per 100-person years, derived from 1.19 [0.51, 2.34] from the tofacitinib placebo group, 4.09 [2.65, 6.04] from baricitinib and 1.75 [0.21, 6.32] from upadacitinib. The estimated IRs were similar in the limited analysis, in which duration of follow up concluded at the point patients randomised to the placebo were crossed over into the treatment arm.

The estimated IRR of SI compared with placebo in per protocol analyses were not statistically significant; 1.22 [0.60, 2.45] for tofacitinib, 0.80 [0.46, 1.38] for baricitinib and 1.14 [0.24, 5.43] for upadacitinib (Figure 28). The pooled IRR for all three JAKi was 0.95 [0.63, 1.44], statistical heterogeneity 0% (95% CI 0% to 84%). Similar findings were seen in the limited analysis (Figure 29). An analysis separating tofacitinib monotherapy from tofacitinib-methotrexate combination studies did not demonstrate a significant IRR of SI compared to placebo (Figure 30).

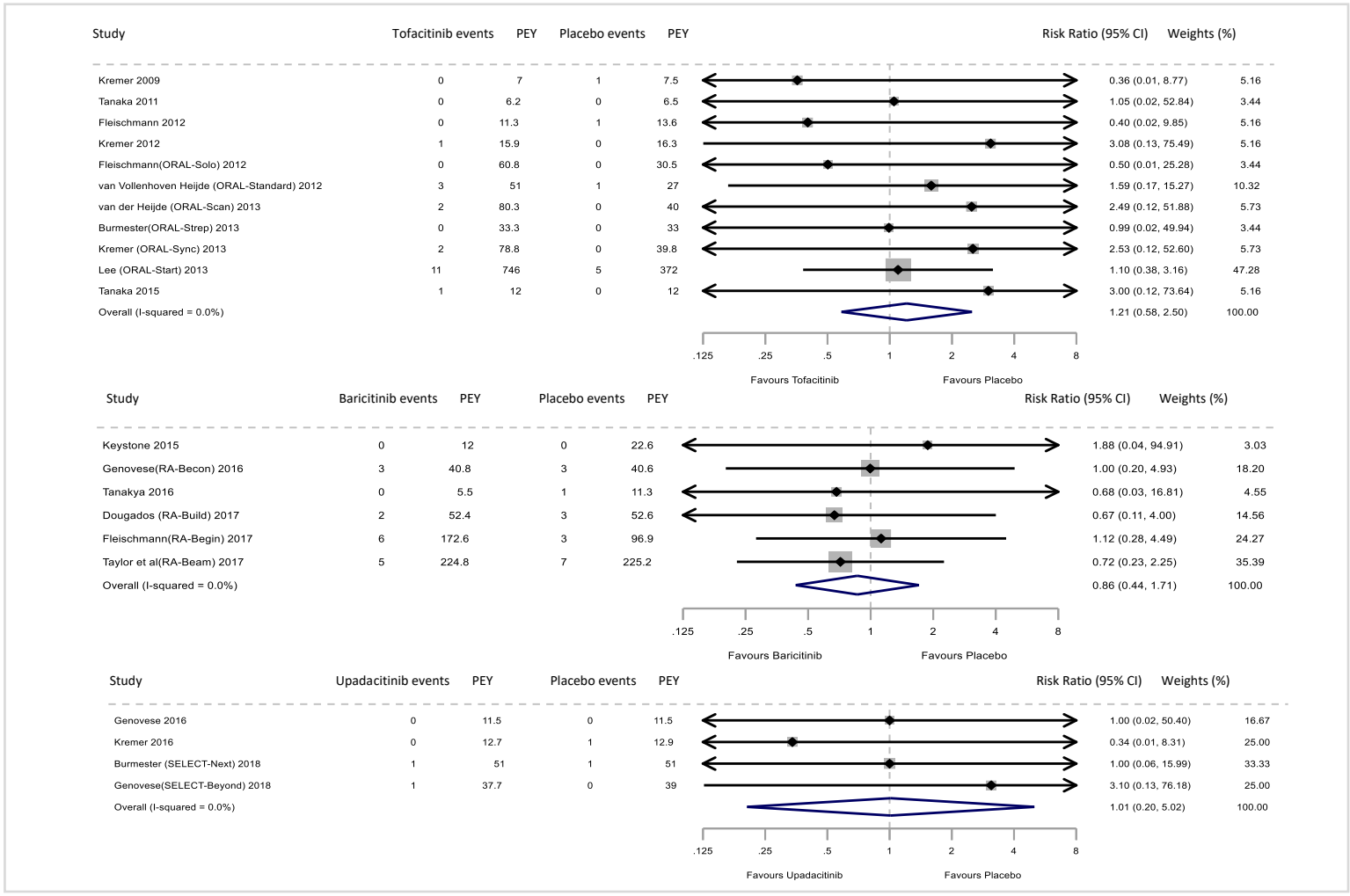
Indirect comparisons between the three JAKi using network meta-analysis did not demonstrated any significant difference in risk of SI (Figure 31). Using the SUCRA approach to rank SI risk, baricitinib was indicated as being associated with the lowest risk of SI and tofacitinib the highest. However due to the high levels of uncertainty in the risk estimates, no clear inference can be made regarding the SI risk, either compared to each other or placebo (Table 44).

Figure 28. Forest plot for incidence rate ratios (IRR) of serious infection between JAKi and placebo



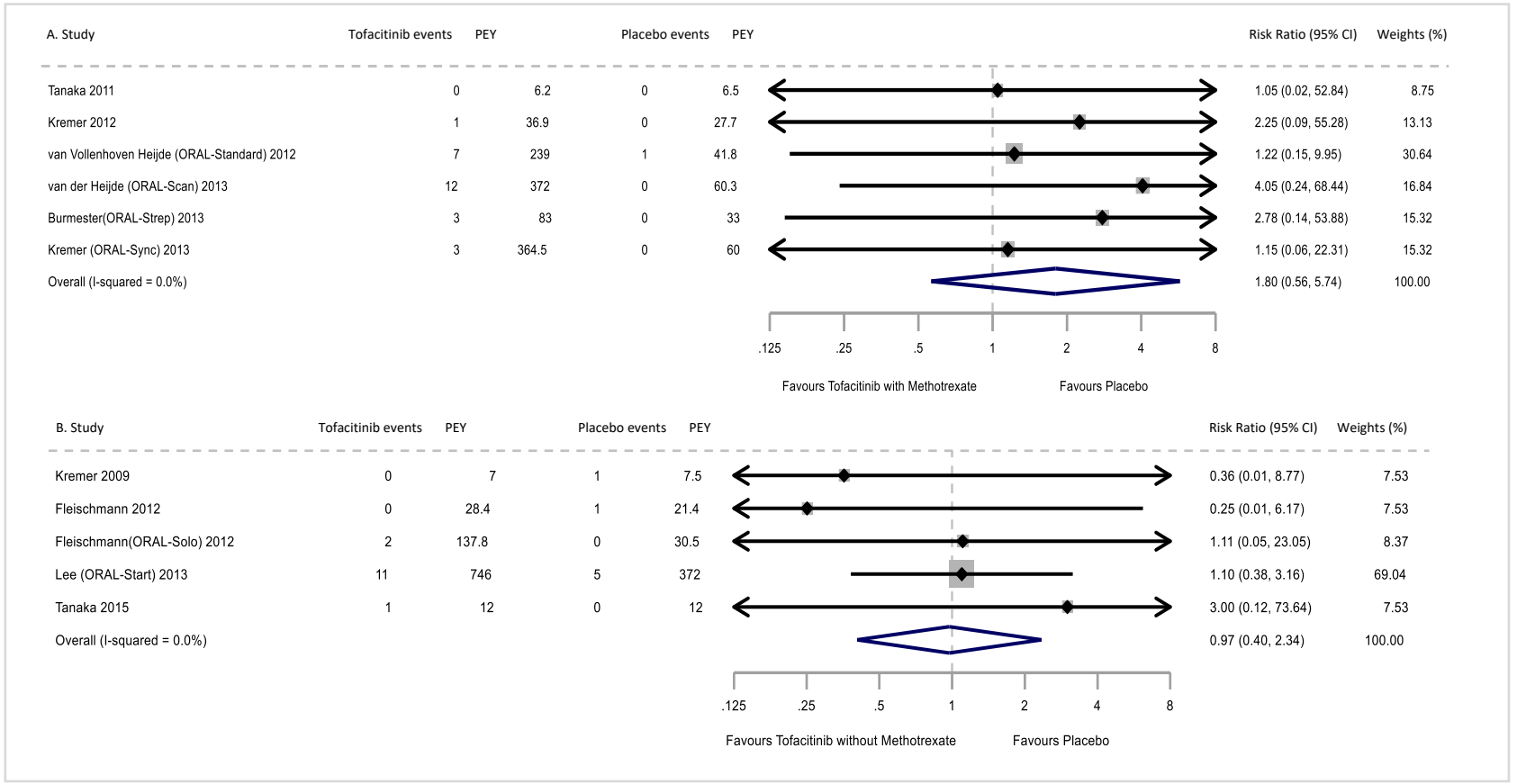
Weights are from Random-effects; 95% CI = 95% Confidence Interval; PEY = Patient exposure years; calculated for all trials.

Figure 29. Forest plot for incidence rate ratios (IRR) of serious infection between JAKi and placebo in sensitivity analysis in which duration of follow up concluded at the point patients randomized to receive placebo were advanced into the active treatment arm.



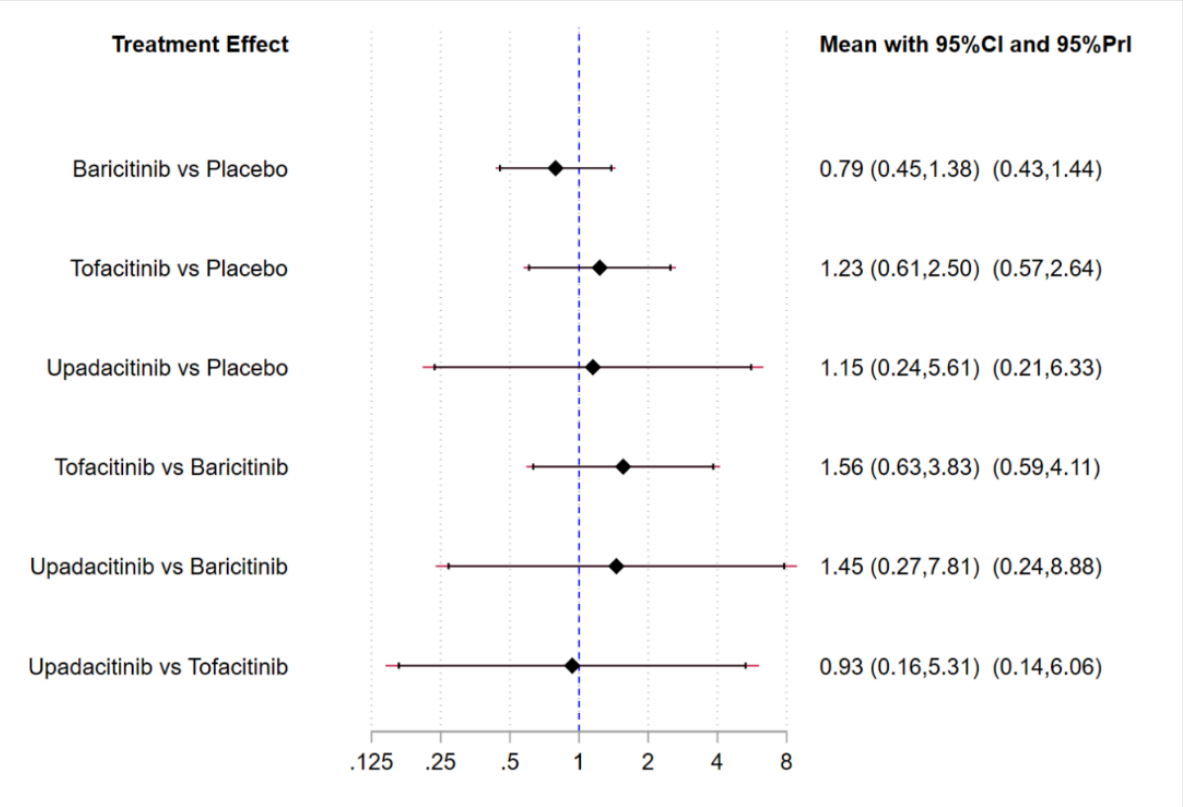
Weights are from Random-effects; 95% CI = 95% Confidence Interval; PEY = Patient exposure years; calculated for all trials.

Figure 30. Forest plot for incidence rate ratios (IRR) of serious infection between JAKi and placebo in sensitivity analysis with tofacitinib (A) in combination with MTX and (B) as monotherapy.



Weights are from Random-effects; 95% CI = 95% Confidence Interval; PEY = Patient exposure years; calculated for all trials.

Figure 31. Network meta-analysis of serious infection with tofacitinib, baricitinib, upadacitinib versus placebo.



Network meta-analysis allow indirect comparisons between the JAKi. As each agent was compared directly with placebo, the relative effectiveness of one JAKi versus another can be estimated indirectly.

Table 44. Surface under the cumulative ranking curve (SUCRA) method to rank serious infection risk

Rank	Placebo	Tofacitinib	Baricitinib	Upadacitinib
Best	9.0	9.0	50.8	31.2
2nd	39.1	15.4	32.0	13.5
3rd	42.6	33.0	11.9	12.5
Worst	9.3	42.6	5.3	42.8
MEAN RANK	2.5	3.1	1.7	2.7
SUCRA	0.5	0.3	0.8	0.4

Each drug was ranked based on the estimated probability of being most effective (causing the least number of SI) under the cumulative ranking curve (SUCRAs). SUCRAs combine the estimated probabilities derived from the NMA, that each treatment is the first best, second best, and so on for all possible ranks. Higher SUCRA values indicate a greater likelihood of a given treatment causing the least number of SI, such that when the SUCRA value is 1, the treatment is certain to be the best, and when it is 0, it is certain to be the worst.

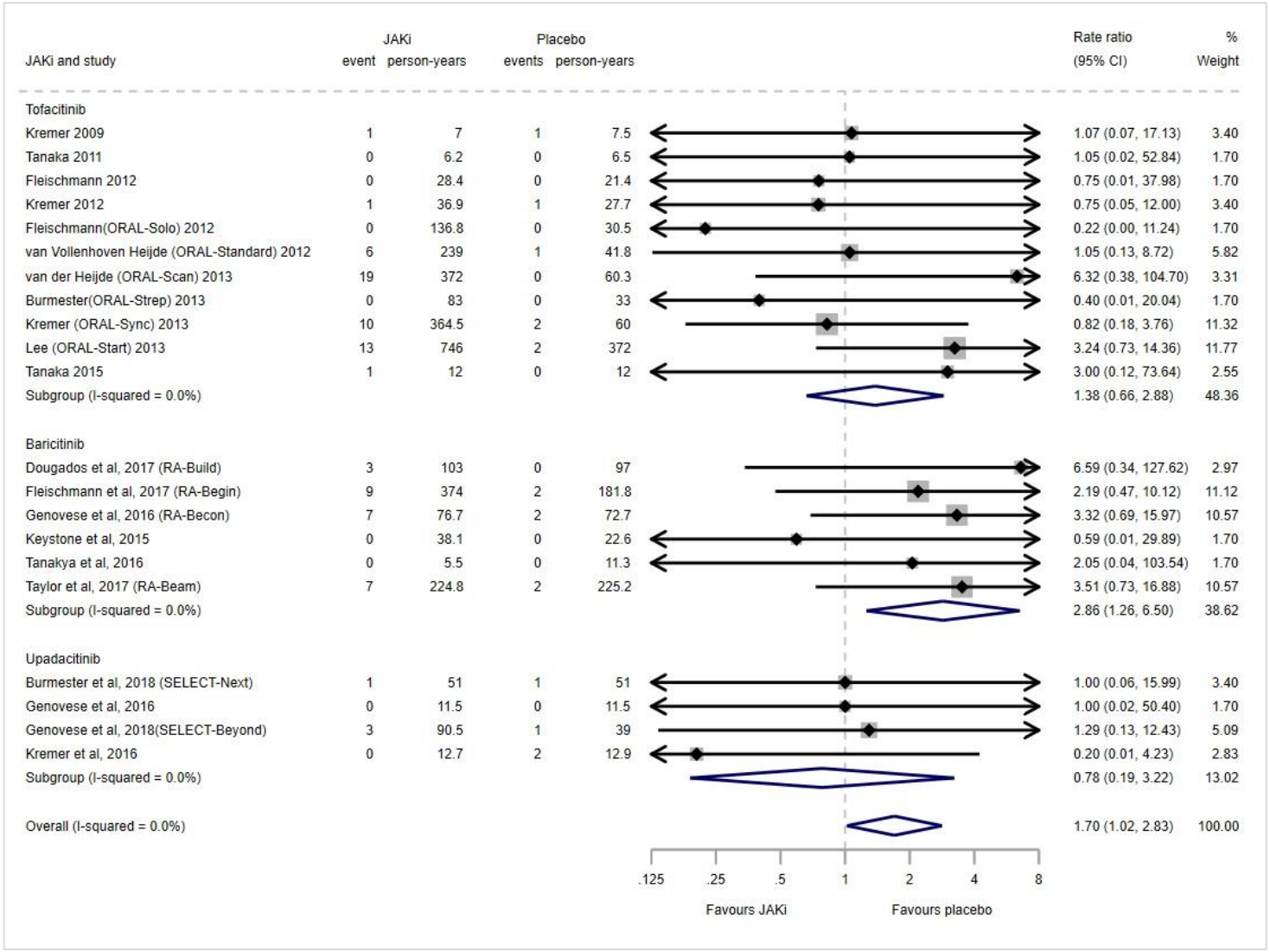
Incidence rates (IR) and incidence risk ratio (IRR) for Herpes zoster (HZ) infection

In the per protocol analysis, there were 51 reported cases of HZ among patients receiving 5mg BID tofacitinib with 2032 PEY; IR 2.51 [95% CI 1.87 to 3.30] per 100 patient-years. There were 26 cases in 822 PEY with baricitinib 4mg; IR 3.16 [2.07, 4.63] and 4 cases in 166 PEY with upadacitinib 15mg; IR 2.41 [0.66, 6.18]. In the pooled placebo group there were 17 cases of HZ with 1398 PEY; IR 1.22 [0.71, 1.95]. There were 8 serious or disseminated cases (4 with tofacitinib and 4 with baricitinib) versus 3 in the pooled placebo group.

The estimated IRR of HZ compared with placebo was 1.38 [0.66, 2.88] for tofacitinib, 2.86 [1.26,6.50] for baricitinib and 0.78 [0.19, 3.22] for upadacitinib, statistical heterogeneity 0% (95% CI 0% to 7.5%) (Figure 32). Similar findings were observed in the tofacitinib-methotrexate combination (Figure 33). However compared to the per protocol analysis, the limited analysis demonstrates marginally larger risk ratios for both baricitinib and tofacitinib (Figure 34). Overall these data indicate a statistically significant difference in the risk of HZ with baricitinib compared with placebo that is not seen with tofacitinib 5mg BID or upadacitinib 15mg BID.

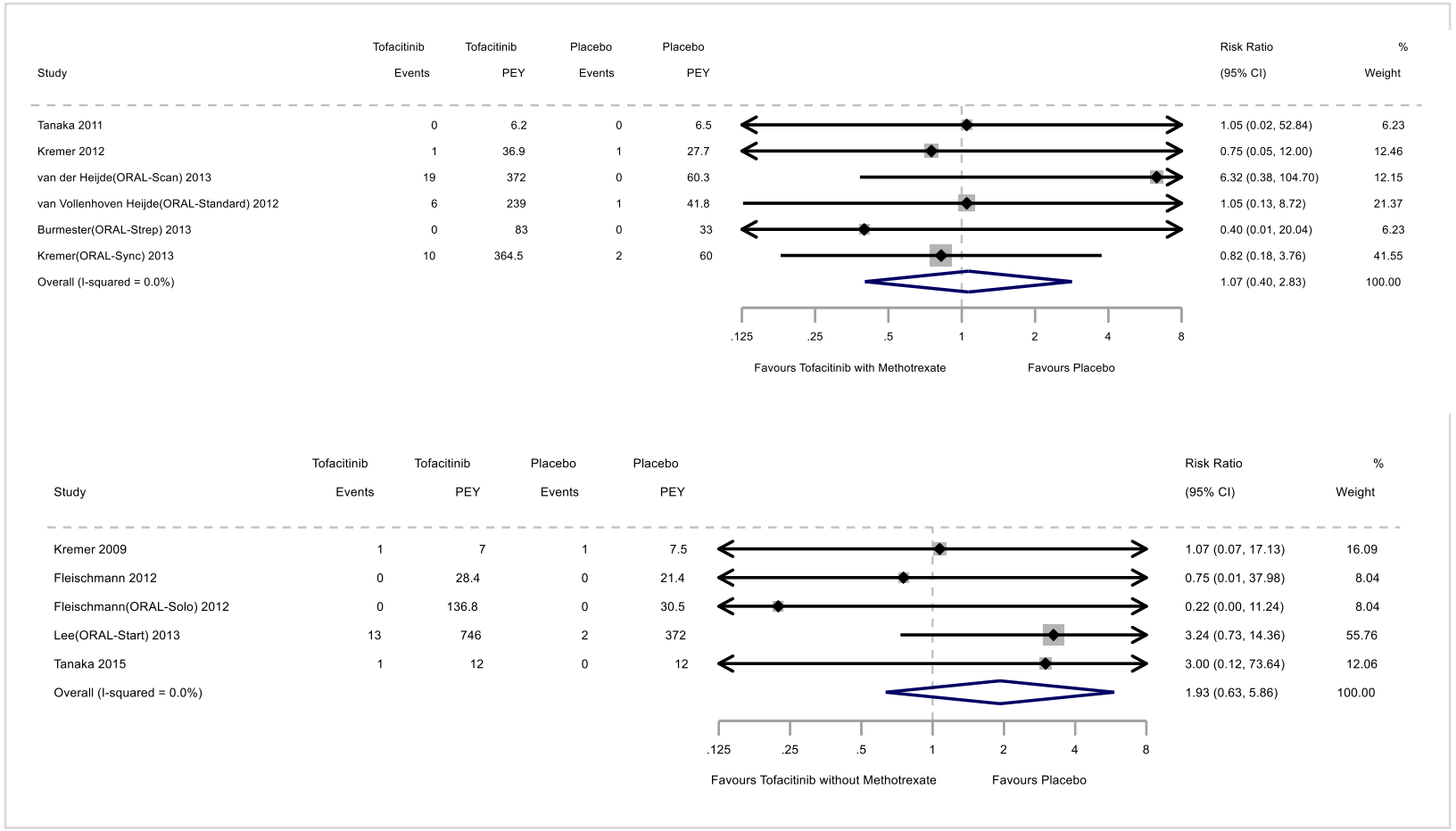
Network meta-analysis confirms a greater risk of HZ with baricitinib than placebo. Indirect comparisons between the three JAKi did not demonstrate notable differences in HZ risk between the drugs (Figure 35). Using the SUCRA approach to rank HZ risk, baricitinib was indicated as being associated with the highest risk of HZ and upadacitinib the lowest. High levels of uncertainty in the risk estimates means no clear inference can be made regarding the HR risk compared to each other or placebo (Table 45).

Figure 32. Forest plot for incidence rate ratios (IRR) of herpes zoster between JAKi and placebo



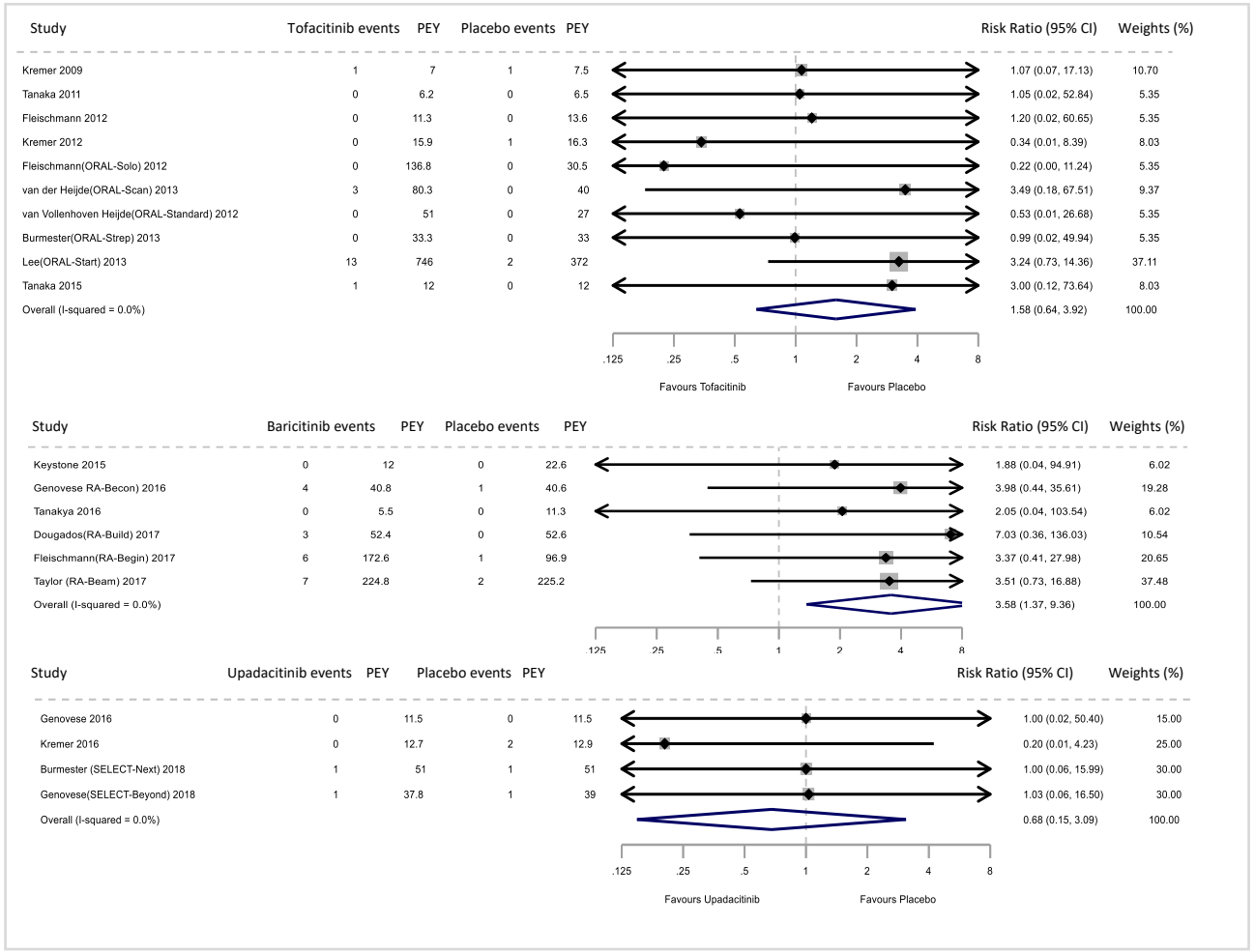
Weights are from Random-effects; 95% CI = 95% Confidence Interval; PEY = Patient exposure years; calculated for all trials.

Figure 33. Forest plot for incidence rate ratios (IRR) of HZ infection between JAKi and placebo in sensitivity analysis with tofacitinib (A) in combination with MTX and (B) as monotherapy.



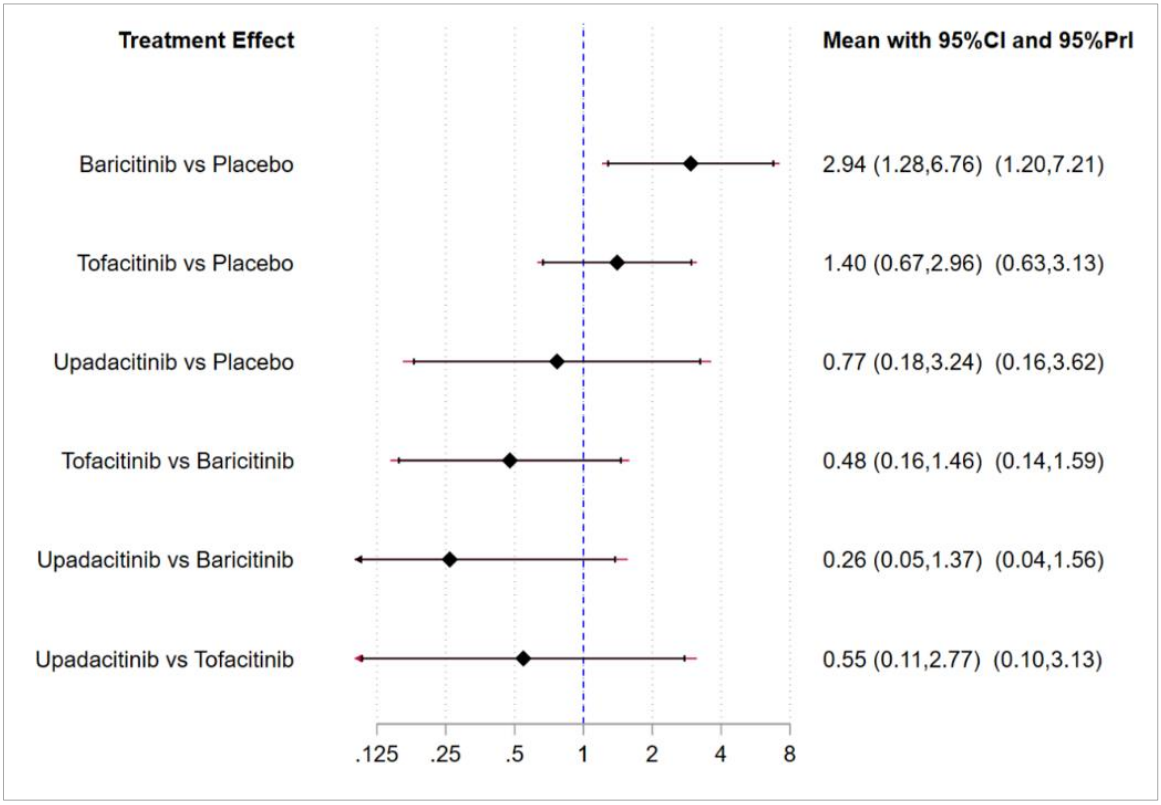
Weights are from Random-effects; 95% CI = 95% Confidence Interval; PEY = Patient exposure years; calculated for all trials.

Figure 34. Forest plot for incidence rate ratios (IRR) of HZ infection between JAKi and placebo in sensitivity analysis in which duration of follow up concluded at the point patients randomized to receive placebo were advanced into the active treatment arm.



Weights are from Random-effects; 95% CI = 95% Confidence Interval; PEY = Patient exposure years; calculated for all trials.

Figure 35. Network meta-analysis of HZ with tofacitinib, baricitinib, upadacitinib Vs placebo



Network meta-analysis allow indirect comparisons between the three JAK inhibitors. As each agent was compared directly with placebo, the relative effectiveness of one JAK versus another, can be estimated indirectly.

Table 45. Surface under the cumulative ranking curve (SUCRA) method to rank HZ risk

Rank	Placebo	Tofacitinib	Baricitinib	Upadacitinib
Best	30.6	6.0	0.4	63.0
2nd	57.6	24.8	1.7	15.9
3rd	11.7	60.7	11.5	16.1
Worst	0.1	8.5	86.4	5.0
MEAN RANK	1.8	2.7	3.8	1.6
SUCRA	0.7	0.4	0.1	0.8

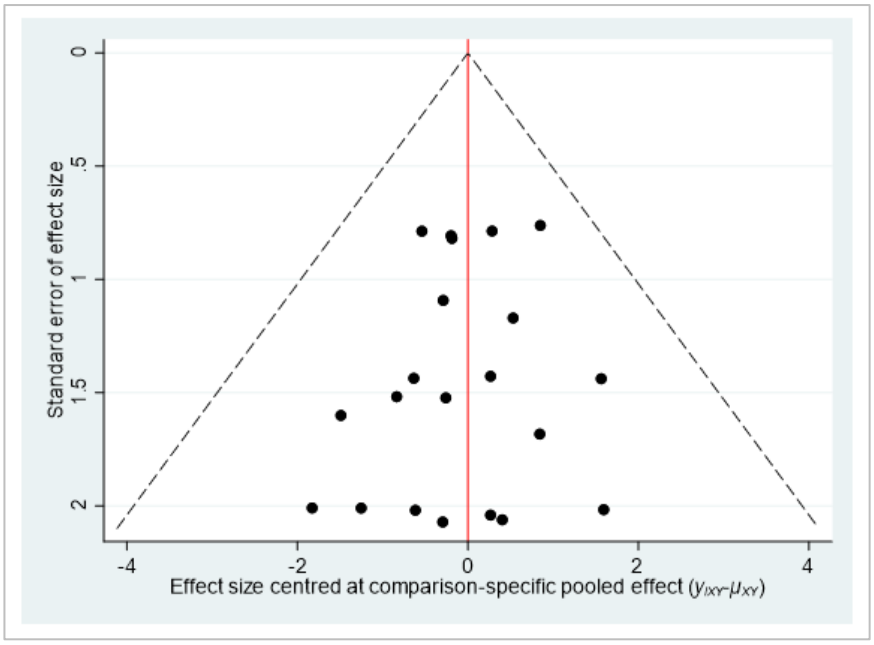
Each drug was ranked based on the estimated probability of being most effective (causing the least number of HZ infections) under the cumulative ranking curve (SUCRAs). SUCRAs combine the estimated probabilities derived from the NMA, that each treatment is the first best, second best, and so on for all possible ranks. Higher SUCRA values indicate a greater likelihood of a given treatment causing the least number of HZ, such that when the SUCRA value is 1, the treatment is certain to be the best, and when it is 0, it is certain to be the worst.

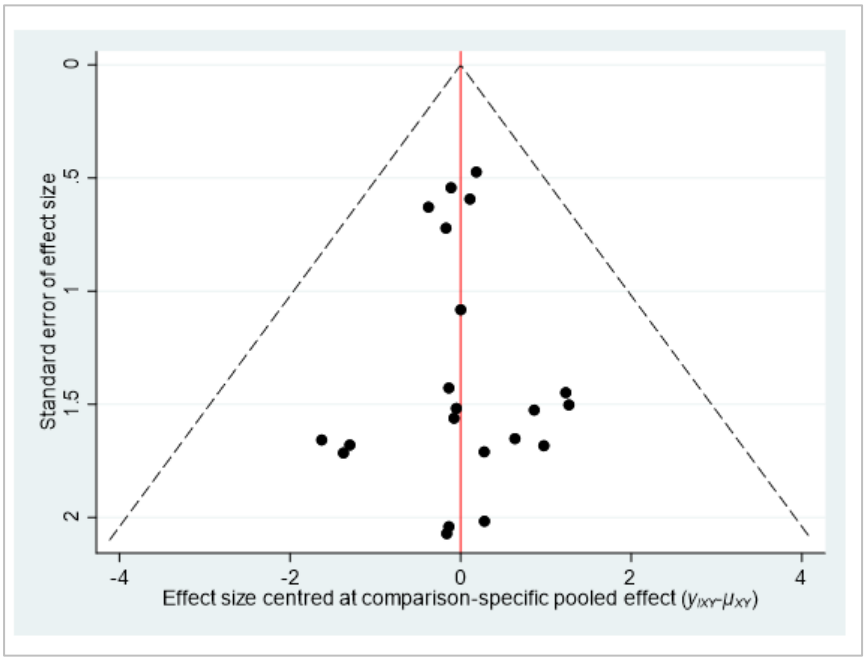
There was no evidence of asymmetry on visual examination of funnel plots for both the SI and HZ analyses (Figure 36). However due to the low incidence rates and large standard errors, it is impossible to rule out a small sample effect such as publication bias.

Indicator opportunistic infections

The incidence rates of opportunistic infections are reported in Table 46. Patients with active or latent *Mycobacterium tuberculosis* (LTBI) were excluded from phase II trials. In phase III studies, patients with LTBI were allowed entry after receiving at least 1 month of a planned 9-month isoniazid preventive regimen. In this analysis there was only 1 episode of tuberculosis in a baricitinib treated patient for whom protocol-defined screening procedures for LTBI had not been fully completed. A combined crude rate of indicator infections excluding HZ was 0.23 per 100 patients' years. The rate of indicator infection was numerically lowest with tofacitinib. With the inclusion of serious or disseminated HZ events, the incidence rate doubled.

Figure 36. Funnel plots examining for publication bias





Funnel plots examining for publication bias for A) serious infection analysis; B) herpes zoster analysis. There was no evidence of asymmetry on visual examination of funnel plots for both analyses.

Table 46. Incidence rates of indicator infections with tofacitinib, baricitinib, upadacitinib and pooled placebo

	Pooled placebo	Tofacitinib	Baricitinib	Upadacitinib
Indicator infection (n)				
Mycobacterium tuberculosis	0	0	1	0
Pneumocystis jirovecii pneumonia	0	1	1	0
Oral or oesophageal candidiasis	2	2	1	1
Hepatitis C	1	0	0	0
Varicella-zoster	1	0	0	0
HZ (*disseminated or serious)*	3	4	4	0
HZ *(non-serious infection)*	14	47	22	4
Patient exposure years	1398	2032	822	166
Incidence rate [95% CI]				
Excluding HZ	0.29 (0.08,0.72)	0.15 (0.03, 0.43)	0.36 (0.08, 1.07)	0.60 (0.02, 3.36)
Including serious / disseminated HZ	0.50 (0.20, 1.03)	0.34 (0.14, 0.71)	0.85 (0.34, 1.75)	0.60 (0.02 ,3.36)
Including all HZ events	1.50 (0.93, 2.30)	2.66 (2.00, 3.47)	3.53 (2.36, 5.07)	2.41 (0.66 ,6.18)

* Incidence rate (per 100 years)

Opportunistic infections were identified from summary data, and categorised as 'indicator' infections from the proposed consensus definition of specific pathogens, or presentations of pathogens that 'indicate' the likelihood of an alteration in host immunity in the setting of biologic therapy (Winthrop et al., 2015b).

8.2.4 Discussion

To my knowledge, this is the first systematic review and meta-analysis reporting on safety of licenced dose JAKi in RA. This work was published in *Rheumatology* in October 2019. This study has demonstrated a greater risk of HZ with baricitinib than placebo, although indirect comparisons between the three drugs did not demonstrate any significant difference in risk.

The absolute event rate for SI were low. The incidence rate ratios comparing to placebo were numerically different between tofacitinib, baricitinib and upadacitinib. However uncertainty in the estimated rates is high due to the rare nature of SI, thus it would be inappropriate to use this numerical difference as evidence of a differential risk between the agents. The placebo cohorts differed in their base incidence rate; tofacitinib 1.19, baricitinib 4.09 and upadacitinib 1.75, which impact the overall incidence rate ratios. This difference in placebo base rate may reflect differences in inclusion criteria, indicating the possibility of selection bias. For example, only 1 of 6 baricitinib studies compared to 4 of 11 tofacitinib studies recruited patients who had received biologics. The SI incidence rate for tofacitinib is lower than that published by Strand and Cohen, with rates of 3.0 and 2.7 per 100 patients' years, respectively (Cohen et al., 2014, Strand et al., 2015b). This discrepancy may be explained by both authors having access to patient-level data and by the inclusion of the 10mg treatment arm and long-term extension studies by Cohen.

The most characteristic infectious complication with JAKi has been the reactivation of VZV. My meta-analysis confirms this signal. The incidence rate of HZ with tofacitinib was lower than that seen with the inclusion of LTE trials and the addition of higher doses (2.1 versus 4.4) (Winthrop et al., 2014). With baricitinib, the rate was similar to that reported in LTE and with higher doses (3.4 versus 3.2) (Smolen

and Genovese, 2018). Across the JAKi, the rate was approximately 3.23 per 100 patient-years. This is higher than that seen with anti-TNF-therapy (1.6) (Galloway et al., 2013a). The rate in the pooled placebo group was 1.05. This is in keeping with rates reported from the UK primary care database, ranging from 0.35 in those under 50 to 1.25 in those over 70 (Forbes et al., 2014).

I demonstrated a significantly increased risk of HZ with baricitinib compared to placebo. A statistically significant increase was not apparent with tofacitinib or upadacitinib, although due to levels of uncertainty in the estimates a true effect cannot be ruled out. Identifying a biologically plausible mechanisms whereby HZ events are higher with baricitinib is challenging, especially since the pathogenesis underlying the risk of HZ with JAKi is poorly understood.

HZ occurs due to reactivation of VZV, which establishes latency in the dorsal root after primary infection (Ku et al., 2004). Cell-mediated immunity plays a greater role than humoral responses in the prevention of VZV reactivation. Declining cell-mediated immunity with age is associated with a reduction in VZV-specific T cells, disrupting immune surveillance and increasing the risk of reactivation. The immune response to VZV is mediated in part via the JAK-STAT pathway. Interferon signalling is essential for both innate and adaptive responses (Arvin, 2008). Type I interferon response is regulated by JAK1-TYK2 complexes and type II interferon mediated via JAK1-JAK2 complexes (O'Shea et al., 2013a, Weinberg and Levin, 2010). Baricitinib demonstrates greater inhibition of JAK2 and TYK2 than tofacitinib or upadacitinib (O'Shea et al., 2013a). Patients with deficiencies in NK cell function experience an extreme susceptibility to infection with VZV. NK development and activation are also dependent on cytokines mediated via the JAK-STAT pathway and a dose-dependent decline in peripheral blood NK cell counts has been reported with all JAKi (van Vollenhoven et al., 2015, Emery et al., 2016, Winthrop, 2017).

The variable pharmacokinetics alongside the possibility of 'pan-JAK' inhibition may explain differences in HZ event profiles with JAKi. The selective targeting of specific JAKs is dose dependent. At higher doses JAKi can block other members of the JAK family, leading to 'pan-JAK' inhibition (Winthrop, 2017, O'Shea et al., 2013a, Clark et al., 2014). In the phase III RCTs, 4mg of baricitinib was considered the higher of the therapeutic doses, whilst 5mg of tofacitinib and 15mg of upadacitinib were the lower treatment doses. This may explain the differences in risk profile of HZ. This potential for 'pan-JAK' inhibition is theoretically higher in routine care patients who have a greater number of co-morbidities and polypharmacy. The metabolism of tofacitinib is primarily mediated by CYP3A4, whilst baricitinib is dependent on renal elimination ((EMA), 16/03/2017, (EMA), 31/03/2017). These pharmacokinetics properties may increase the possibility of dose toxicity and 'pan-JAK' inhibition.

There are several considerations when interpreting these results. The increasing incidence of HZ with age is well recognised. It is a critical confounder and subtle differences in age distribution from these clinical trials could cause significant differences in HZ events. A geographic variation in rates of HZ with JAKi exists, with highest rates seen in Japan and Korea (Winthrop, 2017). This is relevant when examining data extrapolated from studies across different geographical regions. A quarter of the studies in this meta-analysis did not recruit from countries in Asia, which may contribute to a lower overall incidence of HZ. Without patient level data, it is difficult to examine this further. Prednisolone has been consistently shown to increase the risk of HZ by 1.5–2 fold (Smitten et al., 2007a). My ability to evaluate the influence of glucocorticoids is limited; the doses and the total duration of glucocorticoid exposure are not reported in detail and may be a potential confounder.

Indicator opportunistic infection events were too rare to provide meaningful incidence rates. A combined crude rate for all three drugs was 0.23 per 100 patients' years. This is higher than seen with

biological therapy in the UK registry data (0.13) (Rutherford et al., 2018a). The consensus definition of an indictor OI is broader than previous definitions, which may explain differences compared to previous analyses. The main driver of this rate differential is whether the authors considered HZ as an OI or not. There were no cases of tuberculosis in the tofacitinib or upadacitinib trials. This is in keeping with the current literature; cases have been solely in the tofacitinib 10mg treatment arms (Winthrop et al., Cohen et al., 2014). I did not include unlicensed doses in this analysis. Long term extension studies were also excluded from this analysis, which may explain the low event rate, as the median time from commencing tofacitinib therapy until TB diagnosis is 64 weeks (range 15–161) (Winthrop et al.).

There are several strengths of this study. Restricting to licenced doses is of importance. Previous publications have included doses above the licenced level. Unlike biologics, where there is perfect target specificity (i.e. no matter how large the dose, you will only inhibit the TNF activity), with small molecules, the target specificity is dose dependant. Analysing licenced doses reduces the likelihood of detecting signal seen outside the therapeutic window (Hodge et al., 2016).

I acknowledged the escape design employed by most studies. This design influences the incidence of adverse events, since one arm has a continuous exposure to the drug, whereas in the other arm, the exposure is first to placebo and then to drug (Singh et al.). To control for this, I calculated incidence rates using summations of the population exposure risk; a per protocol and a limited analysis were employed. The per protocol strategy may have led to an underestimation of infection risk. Compared to the limited analysis, the per protocol demonstrated a smaller risk of HZ with both tofacitinib and baricitinib compared to placebo. As seen with biological immunosuppression in RA, infection risk is time dependant with the greatest risk early on. The per protocol design includes a longer exposure time to JAKi than to placebo. Lengthening the follow up exposure time would predictably lower the infection

risk estimate. The opposite may hold true when considering other opportunistic infections which take time to establish and correctly diagnose, for example tuberculosis. In this scenario the per protocol strategy may overestimate the infection risk with the JAKi.

There are limitations to this study. Second generation JAKi filgotinib, decernotinib and peficitinib were excluded from the analysis. At the time of writing there were no published phase III trials for these drugs. I felt it was wrong to compare safety data between JAKi that had not been evaluated in phase III trials, as the dose for clinical use has not been delineated. For that reason, it would not be appropriate to comment on the risk of serious infections or HZ with these agents. Of the trials included in the analysis, the sample sizes were relatively small, powered for efficacy and not for the detection of adverse events. Alongside this, the stringent inclusion criteria that is essential for the internal validity of a trial, can limit generalisability to the routine care population. It is possible that differences in infections become more obvious in patients who are at a higher risk and who do not meet the RCT inclusion criteria. The increased risk of HZ with TNF inhibitors was recognised during post marketing surveillance in drug registry data, without a strong signal in phase II and III trials. (Galloway et al., 2013a, Strangfeld et al., 2009b). I acknowledge the background differences in the study placebo rates of infection. As such, the differences seen with infection rates could possibly relate to the study population and not the JAKi. Despite acting as an important framework for identifying serious adverse events, summary data rather than individual level data were aggregated for analyses. This may have resulted in a lack of granularity regarding each infectious event. Lastly, the definition of an indicator infection has only been established in recent years and may have influenced the reporting of OI, resulting in ascertainment bias.

In conclusion, this study has not demonstrated a significant increased risk of SI with licenced dose JAKi compared to placebo. A notable increased risk of HZ with baricitinib was observed. However, the network meta-analysis casts doubt over whether any difference between JAKi are of a magnitude that is clinically meaningful. The imminent publications of active phase III trials with the other JAKi and data from post-marketing surveillance by drug registries, may provide new insights into the differential risk of infections with JAK inhibition, and the mechanisms behind the association with HZ.

Chapter 9. Concluding discussion

Over the last two decades the management of RA has advanced, with vast improvements in clinical outcomes. Treatment paradigms continue to evolve with new NICE guidelines imminently expected. Despite this progress there are many questions that remain unanswered; how to choose the right therapeutic agent for the right patient at the right time. To achieve personalised care in RA we must draw on trial and real-world data to help us better understand clinical phenotypes, to identify those most likely to succumb to adverse outcomes and to avoid causing unnecessary harm to our patients.

This thesis describes several methodologies for analysing patient level data from trials and cohort studies, as well as employing meta-analytical techniques. The most challenging of these were aligned to the BSRBR-RA analyses. Two methodologies were particularly novel, including the use of competing risks survival model in an RA registry context when examining reasons for treatment failure in the elderly, and incorporating single and multiple failure model analytic approaches when interrogating non serious infections.

Defining predictors of disease flare

The study of disease flare in RA is especially topical. Existing trials simply examine disease outcomes at a fixed time point, for example 6 months after initiating treatment, and are agnostic to interim disease fluctuations. In this thesis I have carefully considered flare as a disease outcome, and in doing so have recognised its complexity with multiple driving factors. My research has complemented the body of evidence informing clinicians on the importance of flare and its association with poor clinical outcomes (Morris et al., 2008, Smolen et al., 2019b, Saleem et al., 2012, Markusse et al., 2015a, Ometto et al.,

2016, Myasoedova et al., 2016a). I have contributed to the interpretation of patient phenotypes that predict flare, both in the context of remission and in drug tapering, and have confirmed that laboratory biomarkers are not overtly helpful. This perhaps is a signal of the heterogeneity of flare events, which are not always reflective of immunological disease but may simply reflect symptomatology. Every individual flare is distinctive and so there is no common underlying signature. Another possible explanation is that serum factors are not sensitive enough to detect subtle changes. It would be interesting to consider a more comprehensive search for potential biomarkers by other techniques including RNA sequencing, combined with detailed serial sampling to detect change.

Flares in RA are difficult to measure, with no agreed construct and variable frequency depending on the criteria used to assess them. The advent of wearable digital technology may be a possible solution, providing the opportunity to collect over time and integrate patient generated data. Smart watches or health apps allow us to track symptoms and important outcomes such a physical activity, even providing digital interventions such as behaviour change nudges (Dixon and Michaud, 2018). The Digital Tracking of Rheumatoid Arthritis Longitudinally (DIGITAL) study has just started recruitment, with the objective of investigating the extent to which biometric data correspond with the continuous collection of patient-reported symptoms and outcome measures including RA disease activity and flare (Nowell et al., 2019). A separate randomized controlled trial due to complete this year has analysed a novel mobile app in assessing disease activity between routinely scheduled health care visits (Wang et al., 2018).

This body of work has established that patient reported factors, particularly disability and depression are predictive of flare events, with depression being a novel finding. I acknowledge the strong association between RA and depression burden although it is uncertain which came first - the chicken and egg philosophy. The *Inflamed Mind* research agenda (Haapakoski et al., 2015, Bell et al., 2017,

Miller and Raison, 2016) provides evidence for inflammatory mediators driving low mood, whilst the effects of immunomodulatory therapies correlate with improved mental health measures (Wittenberg et al., 2019). In clinical practice, screening for depression is still not routine. It is not prioritized in major treatment guidelines, and likely underrecognized and sub-optimally managed by healthcare providers (Peterson et al., 2019). Tackling mental health remains a leading priority within the NHS and UK government with current agendas including *Parity of Esteem* and *No Health Without Mental Health*. Translating the findings from this thesis into clinical practice may encourage clinicians to better identify and manage depression, and in doing so improve outcomes for patients with RA.

Identifying predictors of treatment non-response

Treatment outcomes have also been examined in detail in this thesis. I have focused on drug survival and adverse events. Whilst there is no doubt that biologic and targeted synthetic DMARDs are advantageous in the management of RA, it is difficult to separate therapeutic options based on efficacy alone. It has become clear that alternative concepts such as drug survival and safety are equally helpful when deciding on which agent to prescribe for an individual patient.

The UK has an ageing population with nearly 12 million people over 65 years old, and 5.4 million over 75 years old (Coates, 2018). Alongside this, the burden of comorbidity is climbing. Two-thirds of older adults are expected to be living with multi-morbidity by 2035, with 17% diagnosed with four or more diseases (Kingston et al., 2018). However, older individuals and those with significant comorbidities are often excluded from clinical trials. This means that we don't have accurate answers for a large proportion of patients under our care, and perhaps there are adverse factors that go undetected. This is where the science of medicine takes over, as we attempt to apply an evidence base to each individual

we manage. Real world data provides an excellent opportunity to gather further insight regarding this excluded group of patients.

I have considered this issue with two approaches, the first concentrating on age and the second on comorbidity and polypharmacy. For patients with RA, advancing age associates with adverse outcomes. Immunosenescence may explain a greater propensity for infection with higher rates of TNFi discontinuation due to adverse events compared to the younger population. Background crude infection rates increase markedly with age, meaning that absolute risk differences across treatment options become more relevant (Galloway et al., 2011). Immunosenescence may also explain a reduction in immunogenicity. This is supported by the analysis of TNFi monotherapy in the elderly, which demonstrated fewer discontinuations of TNFi due to inefficacy compared to patients receiving combination therapy with methotrexate. This is translatable to clinical practice where it would be reasonable to suggest that we consider using less methotrexate in elderly patients prescribed a TNFi. A major limitation of this analysis, and an alternative narrative would be that we are observing a phenomenon of 'competing risks'. This is where an elderly patient may suffer an adverse event leading to termination of therapy. This removes the patient from the 'risk pool' prior to the outcome of interest, in this case, loss of TNFi efficacy. This should be considered when interpreting these results. Before implementing any change to clinic practice, it is crucial that this research is replicated within other observational studies.

Comorbidity is one of the other key drivers of worse clinical outcomes. Polypharmacy is an attractive surrogate measure of comorbidity. It provides greater granularity than a simple dichotomised 'yes/no' code for an organ-based disease. My research has provided evidence to support the use of polypharmacy readily extracted from routine care datasets for case mix adjustment in epidemiologic

analyses. It is also of direct clinical relevance to practitioners. Every additional medication on a patient's drug chart confers a 13% increased chance of experiencing a serious adverse event. DMARDs should not be incorporated in the count as including them demonstrated numerically lower hazard ratios, although this may reflect a selection bias. During a clinic appointment a medication count can help physicians to personalise care and inform risk assessment. Reducing the number of prescribed medications is unlikely to modify this risk for each individual, however, medicines optimisation, encompassing many aspects of improving medication use, is fundamental to addressing the challenges posed by polypharmacy (Scott et al., 2015, Duerden et al., 2013). This is certainly an interesting area in RA and further research is warranted to explore this.

Treatment related adverse events

Infection is one of the most important adverse events in RA. Many infections are not captured in published observational studies which historically only examined 'serious' events. Frequent non serious infections including influenza, sinusitis, cellulitis and UTIs, are often managed in an outpatient setting. Although not life threatening these events have considerable impact on the individual, contributing to work disability, poor quality of life, RA disease flare and treatment discontinuation.

In this thesis I have quantified the burden of these events, which occur frequently - affecting more than 1 in 10 patients annually. For every 100 patients there are 27 NSI events per year. Biologic treatment strategies are associated with these events. Tocilizumab demonstrated the highest risk of non-serious infection, which is consistent with findings from serious infections analyses (Rutherford et al., 2018c). Likewise, other predictors of non-serious infection including increasing age, comorbidity, corticosteroid therapy, RA disease activity and disability are similar to those observed with serious infection (Doran et al., 2002b, Au et al., 2011, van Dartel et al., 2013b). The magnitude of effect for steroid was small;

however steroid data were established on baseline information only and coded in a binary manner. Parallel steroid research published recently confirms a strong association with serious infection, with a magnitude of risk with doses of less than 5mg/day that is similar to that observed with biologics (George M, 2019). In clinical practice, the results from my research will allow us to quantify the burden of non-serious infections with our patients, address factors that may escalate their risk and permit open dialogue considering choice of therapies.

Unfortunately, I could not explore the impact of JAK inhibition on non-serious infection. This is highly relevant as JAK inhibitors have emerged as an important risk for herpes zoster, often managed as an outpatient non-serious event. As these agents have only recently been licenced in the UK, the number of patients recruited to JAKi drug cohorts within the BSRBR-RA were too small to interpret at the time of analysis.

JAK inhibition in RA is attracting growing attention with impressive results from phase III studies. These therapies, in particular the selective JAK1 inhibitors, demonstrate notable efficacy with a significant proportion of patients achieving remission at just 12 weeks (Fleischmann et al., 2019). The EMA has recently concluded that tofacitinib should not be used in patients older than 65 years of age unless there is no alternative treatment. These recommendations follow a review of an ongoing safety study (ClinicalTrials.gov Identifier NCT02092467) comparing 5mg and 10mg tofacitinib with adalimumab and etanercept in patients > 50 years old with cardiovascular risk factors. Results demonstrated an increased risk of serious and fatal infections in patients over 65 years of age.

Although crucial safety data are generated from clinical trial and long-term extension studies, these are underpowered to scrutinise rare events like shingles. Meta-analyses are valuable in assembling

evidence from multiple clinical trials, enhancing overall power and constructing a pooled effect estimate. My systematic review and meta-analysis of infection risk with JAK inhibitors in RA was contemporary, innovative and published during a period of increasing relevance. This research confirms a low serious infection rate, but an incidence of herpes zoster that is higher than expected in the RA population. Although the risk is greatest with baricitinib, differences between agents are not statistically significant, and the signal is likely to be a 'class effect'. This risk should be conveyed in clinical practice with counselling offered to patients starting therapy and consideration to avoid a JAK inhibitor in certain patients. At present, there is little evidence base around risk mitigation. A live-attenuated vaccine (Zostavax, Merck) is licensed for adults over 50, although contraindicated in immunosuppressed individuals. A recombinant subunit vaccine has demonstrated superior efficacy although a greater risk of injection site adverse events (Tricco et al., 2018). Studies on its immunogenicity and efficacy in immunosuppressed patients are scarce. A study investigating this vaccine in RA patients treated with JAK-inhibitors has just started recruiting and is due to complete in 2021 (ClinicalTrials.gov Identifier NCT03886038).

Future work

When considering my future research plans, I would like to better understand the grading of infectious events for patients receiving immunomodulating therapies. The current dichotomised classification system lacks granularity and may have contributed to an underreporting and disregarding of non-serious events. There are no other universally established infection severity classification or grading systems. A new classification tool to characterise infectious events would be useful in trial and epidemiological research and prove a valuable tool in clinical practice to aid treatment decisions. To this end, I have employed a Delphi exercise to achieve consensus opinion from real-world knowledge, solicited from experts (work in progress). This is a widely accepted technique in areas where the

evidence base falls short. The Delphi is split into several rounds allowing responses to be refined via multiple iterations into a set of specific statements or variables based on pure consensus. This process will require careful consideration, as the variables included in a new infection classification system will impact future data collection and may restrict the use of certain observational datasets when validating the score.

I would also like to further examine treatment related adverse events with JAK inhibition within the BSRBR-RA. In these analyses I would focus on all infection in patients over 65 years old, and non-serious infections specifically herpes zoster. Furthermore, I would like to observe the impact of non-serious infection on long-term outcomes including drug efficacy and discontinuation.

Finally, I would like to identify if RA disease specific factors associate with infection risk. The current dogma is that infection is a result of the "immunosuppressive" therapeutic agents used to treat the condition. However, we acknowledge that disease itself likely plays a key role, with evidence for certain immunologic alterations associated with RA perturbing host defence against foreign pathogens. Disturbances of both the innate and adaptive immune system are thought to contribute, although early studies have not indicated numerical cellular defects e.g. neutropenia or reduction in T lymphocytes to be predictive of infection. Research into plausible cellular biomarkers of infection would be fascinating. I am fortunate to have access to the TACERA (Towards A Cure in RA) dataset. This longitudinal study recruited newly diagnosed RA patients and prospectively captured all infective episodes with a novel infection proforma to a level of detail normally afforded to trials of interventional medicinal products. During the study period, peripheral blood samples were collected at multiple visits which have been primed for extensive immune phenotyping and transcriptomic analysis. My analyses will comprise examining flow cytometry profiles and modules of co-ordinately expressed transcripts focusing on

inflammation and infection related genes. The objective would be to identify cellular and molecular signatures that associate with infection in RA, to ascertain a biomarker that might identify patients at highest risk. The surveillance of immunomodulating therapies via drug registries has permitted the identification of clinical phenotypes that predict infection. Our current understanding of immune signatures of infection risk is limited and this work may prove valuable to the rheumatological world, but also to a wider audience considering the recent COVID-19 pandemic.

Summary

In summary, my research has enhanced our understanding and knowledge surrounding the efficacy and safety of targeted therapy for patients with RA. This work could directly influence clinical practice, with the long-term goal of reducing adverse outcomes. RA remains an incurable disease. Whilst we have effective therapeutic options, we must recognise the risks and benefits of these agents at an individual level and engage our patients in shared decision making. My research has complemented the epidemiologic methodologies applied to BSRBR-RA analyses and is transferable to other pharmacological observational datasets.

In this area of RA research, there remain unanswered questions. It is a field with fast evolving therapeutics and extensive drug development programmes. Real world studies will always remain one step behind. As it stands, data on the efficacy and safety of JAK inhibitors in clinical practice are limited. With the increasing use of these agents, there is greater opportunity to study them in observational cohort and drug registries. Dedicated research using real world data would provide answers for many unresolved issues. Furthermore, we live in an evolving digital age with advances in technology that have transformed healthcare. We should embrace the opportunities that emerge, specifically the capturing of adverse events like infection. With enumerable issues in collecting outcomes on non-

serious infection, a possible digital solution exists. Using patient generated data from remote monitoring by smart phones or wearable devices may revolutionise research in this field.

Appendices

Other related publications

Bechman K, Dalrymple A, Southey-Bassols C, Cope AP, Galloway JB. A systematic review of CXCL13 as a biomarker of disease and treatment response in rheumatoid arthritis. Accepted BMC Rheumatology

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