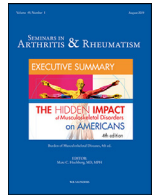Contents lists available at ScienceDirect

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C-reactive protein and implications in rheumatoid arthritis and associated comorbidities

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A B S T R A C T

C-reactive protein (CRP) is routinely assessed as a marker of systemic inflammation in rheumatoid arthritis (RA). However, it is also an immune regulator that plays an important role in inflammatory pathways associated with RA and promotes atherogenic effects. Comorbidities linked to systemic inflammation are common in RA, and CRP has been associated with the risk for cardiovascular disease, diabetes, metabolic syndrome, pulmonary diseases, and depression. The relationship between systemic inflammation, CRP, and comorbidities in RA is complex, and it is challenging to determine how changing CRP levels may affect the risk or progression of these comorbidities. We review the biological role of CRP in RA and its implications for disease activity and treatment response. We also discuss the impact of treatment on CRP levels and whether reducing systemic inflammation and inhibiting CRP-mediated inflammatory pathways may have an impact on conditions commonly comorbid with RA.

Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated systemic inflammatory disease characterized by chronic synovial inflammation and hyperplasia, which drive joint erosion and damage, and a range of systemic manifestations, which contribute to overall disease burden [1]. This results in functional decline, disability, and reduced quality of life for patients with RA, particularly due to symptoms such as pain, fatigue, and morning stiffness [1−5]. Comorbidities are common in RA and require a holistic management approach, as multiple comorbidities are associated with poorer clinical outcomes [6−8]. Patients with RA have an almost 2-fold higher cardiovascular (CV) risk than the general population, [9,10] and more than 50% of premature deaths among RA patients are due to CV disease (CVD) [11].

Proinflammatory pathways result in localized joint and systemic inflammation, [1] with cytokines, such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), IL-1β, as well as downstream signalling pathways, eg, the Janus kinase (JAK)/signal transducers and activators of transcription pathway, playing important roles [1,12,13]. One function of IL-6 is to drive production of the acute-phase reactant C-reactive protein (CRP) following an inflammatory event [14−16]. While CRP is a key marker of systemic inflammation in RA, its overarching

role in RA and its association with comorbidities has not been comprehensively investigated. In this narrative review, we discuss the role of CRP in RA, focusing on the relationship between CRP and comorbidities, and the effect of RA treatment on CRP levels and outcomes. Articles were identified in PubMed using search terms CRP and RA together with: comorbidity, anaemia, asthma, cancer, chronic obstructive pulmonary disease (COPD), CVD, diabetes, interstitial lung disease (ILD), disease-modifying anti-rheumatic drug (DMARD), methotrexate, TNF inhibitor (TNFi), IL-6, JAK inhibitor, and steroids. Results were limited to articles in English published in the last 10 years and supplemented by inclusion of relevant citations found within identified articles.

Roles of CRP in RA

In general, CRP plays an important role in host defence mechanisms against infectious agents and in the inflammatory response. [17,18] CRP binding to immunoglobulin Fc gamma receptors (FcγR) promotes the production of proinflammatory cytokines leading to an amplification loop of inflammation [27−29]. It is produced predominantly by hepatocytes in response to stimulation by IL-6, [14,15] but CRP has also been reported to be expressed by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes (Fig. 1) [18]. A significant correlation has been seen between serum CRP levels and tissue inflammation scores from knee synovium biopsy samples in patients with RA ($n = 197$; $p < 0.0001$) [46]. Analyses of serum

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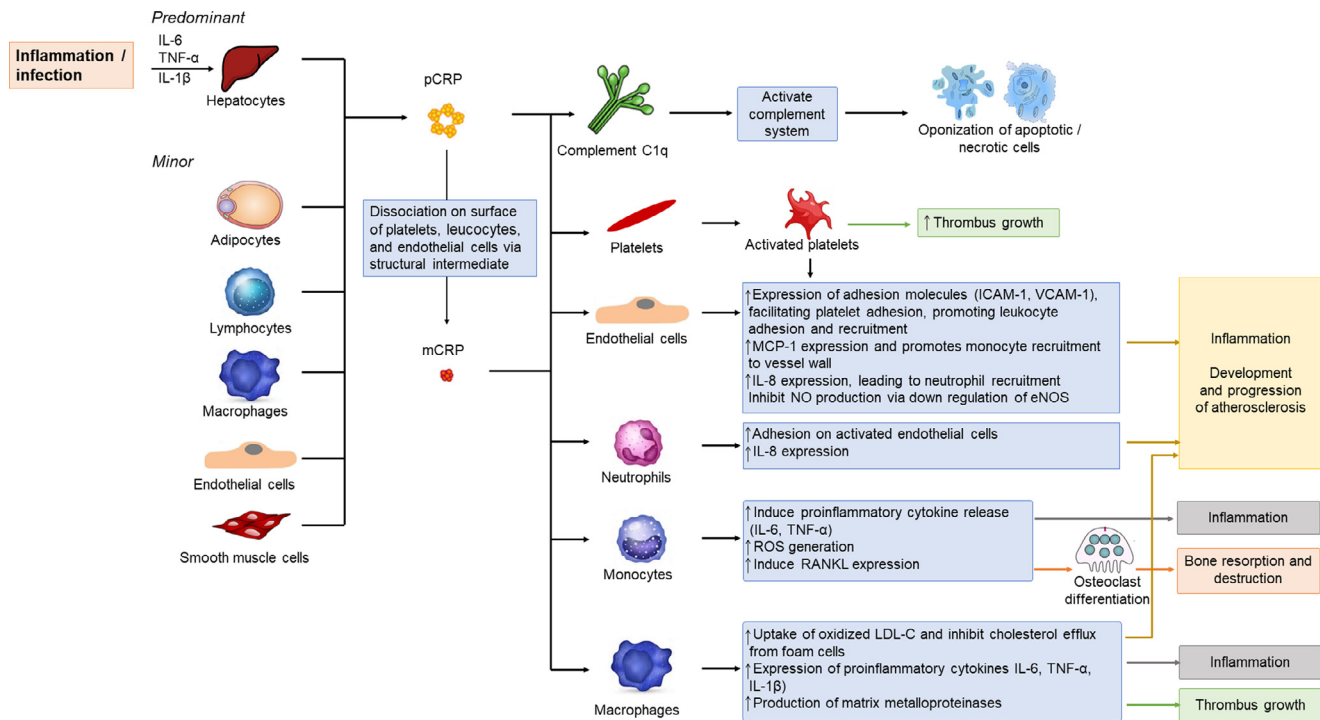*E-mail address:* ChoyEH@Cardiff.ac.uk (E.H. Choy).

Fig. 1. The biological role of C-reactive protein (CRP).

C1q, complement component 1q; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; mCRP, monomeric CRP; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; pCRP, pentameric CRP; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species; TNF, tumour necrosis factor; VCAM-1, vascular cellular adhesion molecule-1.

and synovial fluid CRP in patients with RA have shown that CRP levels closely correlate with IL-6 levels [19−23].

CRP is an immune regulator − not just a marker of inflammation or infection [17,18]. There has been controversy over the direct role of CRP in inflammation and infection, but the identification of CRP isoforms with different biological properties provided a potential explanation for conflicting observations [24]. CRP is synthesized in hepatocytes and secreted into the circulation as pentameric CRP (pCRP), also known as native CRP. pCRP is thought to act as an immune regulator [25]. When bound to cell membranes or liposomes, pCRP can irreversibly dissociate via a conformationally changed intermediate into monomeric CRP (mCRP), which is a proinflammatory isoform able to activate platelets, leucocytes, and endothelial cells as well as bind complement component 1q to activate complement [18,25,26]. mCRP has limited solubility compared with pCRP and is considered to be tissue bound, although transmission via microparticles and ligand complexes has been postulated [25]. Depending on its structural form, CRP interacts with a variety of leucocytes and endothelial cells, stimulating proinflammatory cytokine release, including IL-6, IL-1β, and TNF-α, upregulating adhesion molecules, increasing monocyte chemoattractant protein-1 release to recruit monocytes, inhibiting nitric oxide production, and activating platelets, thereby inducing proinflammatory and atherogenic effects (Fig. 1) [18,24,26−30]. Reference to CRP hereafter signifies circulating CRP without distinction between isoform unless specified.

Circulating CRP levels

In healthy adults, plasma CRP concentration is usually <10 mg/L, although there is considerable inter-individual variability [17,31,32]. CRP levels >10 mg/L are generally considered elevated, although the normal reference range can differ between assays [33]. Obesity is associated with elevated CRP levels. [34] Serum CRP levels can be tested using standard or high-sensitivity (hsCRP) assays; hsCRP is

used for evaluation of conditions potentially associated with inflammation in otherwise healthy individuals [33].

CRP levels are often persistently elevated in patients with RA, with levels of >20 mg/L frequently reported at baseline in randomized clinical trials (RCTs) of drugs to treat RA [35]. However, retrospective and observational real-world studies show that many patients have normal CRP levels despite exhibiting RA disease activity, [36,37] suggesting that CRP levels reflect only one of the signs of disease activity and should be assessed in the context of other measures. Additionally, multiple factors influence baseline serum CRP levels in patients with RA. Single nucleotide polymorphisms in CRP and their haplotypes have been associated with higher or lower CRP levels, [38−40] although no association was found in a prospective observational study of a patient population with much higher average baseline CRP levels (34 mg/L) [41]. Body fat, female hormone levels, dietary quality, and stress have also been shown to influence CRP levels in patients with RA [42−45]. As pharmacological treatments for RA reduce systemic inflammation, CRP levels generally decrease with treatment, to differing degrees depending on the drug class and mechanism of action.

Biological effects of CRP in RA

There is growing preclinical evidence that CRP may play a direct role in bone destruction in RA. Bone destruction is initiated via induction of receptor activator of nuclear factor-κB ligand (RANKL) expression, which stimulates osteoclastogenesis, resulting in bone-resorption. CRP induces RANKL expression in peripheral blood monocytes and stimulates osteoclast differentiation in the absence of RANKL [20]. However, the effects of CRP on osteoclast differentiation might depend on CRP isoform. mCRP has been shown to inhibit RANKL-induced osteoclast differentiation in vitro, by neutralizing RANKL, potentially exerting a protective effect [47,48]. Additionally, patients with RA who have a monocyte imbalance (M1/M2 ratio >1) exhibit significantly higher levels of CRP than those with M1/M2 ratio

≤1 (4.5 versus 0.8 mg/L; $p = 0.032$) and greater in vitro osteoclasto-genesis [49]. More research is needed to fully elucidate the role of CRP in bone destruction.

CRP as a marker of RA disease activity

Higher CRP levels are associated with greater RA disease activity based on the core components of the 28-joint Disease Activity Score (DAS28) [50,51]. Individual aspects of disease activity, such as swollen joint count, and patient-reported measures, including functional status (Health Assessment Questionnaire score), morning stiffness, fatigue, and pain, have also been associated with CRP [52−56]. Indeed, CRP levels are widely used for monitoring systemic inflammation and disease activity in RA. CRP level is a component of several composite disease activity measures: DAS28-CRP, SDAI, and American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) definitions of remission. [57−59] Yet, the usefulness of CRP testing as a routine measure of RA disease activity is not universal due to the substantial proportion of treated patients who experience flares in their RA but still have normal CRP levels. In fact, as RA clinical trials often specify elevated CRP (for example ≥6 mg/L) [60] as an eligibility criterion, patients with active RA but without elevated inflammatory markers are commonly excluded.

Along with disease activity, CRP is known to be associated with radiological damage in RA. Numerous studies in patients with early RA have shown that elevated CRP levels both at baseline and using time-integrated measures correlate with rapid radiological progression and joint damage within 1 year. [61−66] Elevated baseline CRP levels are also a more general predictive factor for radiographic progression and joint destruction in patients with early, moderate and severe RA [64,67,68]. However, a CRP threshold level that could be used as a marker for radiographic progression has not been established.

As noted above, CRP is a standard component of many RA composite disease activity measures (DAS28-CRP, SDAI, ACR/EULAR remission) [57−59]. ACR and EULAR recommend DAS28 using either CRP or erythrocyte sedimentation rate (ESR) without differentiating between them in terms of disease activity thresholds [57]. However, there is evidence that DAS28-CRP scores are consistently lower than DAS28-ESR values [187−189]. Given disease activity thresholds (high >5.1, low disease activity [LDA] <3.2, and remission <2.6) were originally validated using DAS28-ESR, using the same thresholds for

DAS28-CRP may underestimate residual disease activity [187,189]. Consequently, new disease activity thresholds for DAS28-CRP of >4.6, <2.9, and <2.5 have been proposed. [187,189] Additionally, there may be challenges in assessing remission with DAS28-CRP when patients are treated with IL-6 inhibitors and other drugs that directly affect levels of CRP, as a reduction in CRP may not reflect a decrease in disease activity. Thus, a more stringent threshold for DAS28-CRP remission of <1.9 has been proposed [190]. Moreover, many patients with active RA may not have an elevated CRP and this is a common reason for screen failures in RA treatment trials [36,191].

Association of CRP with comorbidities in RA

There is a high prevalence of comorbidities in patients with RA, the most common of which include CVD, metabolic syndrome, diabetes, pulmonary diseases, and depression [6]. While the biological relationships between CRP levels and comorbidities in RA have not been fully established, elevated CRP levels have been shown to be associated with an increased risk for several common comorbidities (Fig. 2). Understanding these associations is important from a clinical perspective to help in the identification of patients at risk for comorbidities, especially those that may be associated with an increased risk for mortality.

Cardiovascular comorbidities

Data from large observational cohorts have shown that RA is associated with an up to 2-fold increased CV risk compared with the general population, [9,10,69,70] including reported increased risks of myocardial infarction (MI; 33−96%), [70−72] heart failure (61−87%), [70,72] stroke (24−29%), [71] and major adverse CV events (MACE; 30−58%), [71,73] along with a 50% higher incidence of CV-related mortality, [71,74] independent of traditional CV risk factors. In a meta-analysis, the relative risk for patients with RA to develop CVD was age dependent, with higher CV risk seen in patients aged <50 than 50−65 or >65 years (risk ratio (RR) 2.59, 1.86, and 1.27 versus the general population). [75] Moreover, there is evidence from epidemiological studies of a strong association between CRP and IL-6 levels and CV risk. [76−79] In the general population, CRP is considered an independent predictor of CV risk, [80,81] with a 58% increased risk for coronary heart disease with CRP levels >3.0 versus <1.0 mg/L
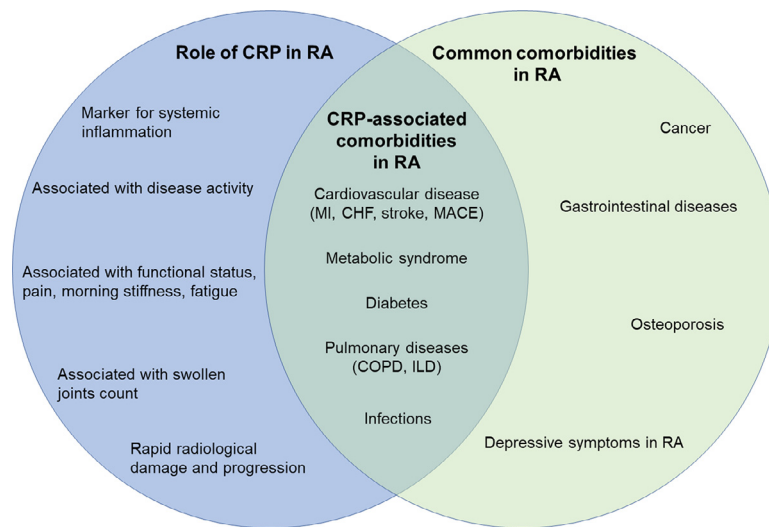

Fig. 2. The interplay of C-reactive protein (CRP) and common comorbidities in RA.
CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HBV, hepatitis B; HCV, hepatitis C; ILD, interstitial lung disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; RA, rheumatoid arthritis.

[80]. CRP is also a predictor of CV risk in RA. Large observational cohort studies have reported associations between elevated CRP levels in RA and a more atherogenic lipid profile and hyperlipidaemia, [83,84] an increased risk for MI (hazard ratio [HR] 2.12, 95% CI 1.02−4.38 for CRP >10 versus <1 mg/L), [85] heart failure (HR 1.25, 95% CI 1.06−1.48 per 100 mg/L increase in CRP), [86] stroke (HR 2.02, 95% CI 1.32−3.08 for CRP >21.7 mg/L versus <2.6 mg/L), [87] and CV-related death (14% increase for each mg/L and HR of 3.3 [95% CI 1.4−7.6] for CRP ≥5 mg/L) [88,89]. Higher CRP levels also increase risk for atherosclerosis and increase subclinical atherosclerosis as measured by carotid intima media thickness in patients with RA [90−94].

Systemic inflammation is a key driver of atherosclerosis. Specifically, CRP has been shown to have a direct biological role in the development and progression of atherosclerosis and thrombosis [82]. CRP increases during the progression of atherosclerosis and can activate the complement system, inducing apoptosis, and contributes to endothelial dysfunction by inhibiting nitric oxide and upregulating endothelial cell adhesion molecules. It also promotes monocyte recruitment into atherosclerotic plaques and increases the inflammatory response by inducing leucocyte adhesion and migration and generation of reactive oxygen species (Fig. 1). CRP also contributes to plaque instability by inducing metalloproteinase expression and promotes thrombus growth via induction of platelet activation.

A reduction in disease activity in RA has been shown to be associated with a reduction in CV risk in numerous studies. Indeed, data from the longitudinal CORRONA registry demonstrated that a 10-point reduction in time-averaged CDAI was associated with a 21% decrease in CV risk [95]. In a meta-analysis of clinical studies, methotrexate and TNFis each appeared to reduce the CV risk by approximately 30% (RR 0.72, 95% CI 0.57−0.91, p = 0.007 and RR 0.70, 95% CI 0.54−0.90, p = 0.005, respectively) [96]. Abatacept showed a modest reduction in risk for a composite CV endpoint compared with TNFis in a large population-based RA cohort (HR 0.86, 95% CI 0.73−1.01) [97]. Despite the known effect of IL-6 inhibitors for increasing lipid levels, [98] in the randomized, open-label ENTRACTE trial, the estimated risk for MACE was similar between tocilizumab (an IL-6R inhibitor) and etanercept (HR 1.05, 95% CI 0.77−1.43) [99]. Likewise, an integrated safety analysis of clinical trials of the IL-6R inhibitor, sarilumab, reported exposure-adjusted incidence rates of MACE of 0.2−0.5/100 patient-years, comparable to the incidence in the general RA population (1.2/100 patient-years) [100]. Pooled safety analyses for JAK inhibitors report similar incidence rates of MACE for tofacitinib of 0.4/100 patient-years and baricitinib (4 mg) of 0.8/100 patient-years. [101,102] Further research is needed to determine whether the biological link between elevated CRP in RA and in CVD and the reduction in CRP levels during treatment for RA contributes to the reduction in CV risk reported in these studies.

Metabolic syndrome

The prevalence of metabolic syndrome appears to be greater in patients with RA than the general population, with rates of 30−40% reported compared with about 20% in controls [103−107]. Higher CRP levels have been associated with increased prevalence of metabolic syndrome in RA, [107,108] greater abdominal adiposity, [109] decreased insulin sensitivity, [110−114] and increased lipid levels [83]. However, two North American cross-sectional cohort studies did not find a significant association between CRP and metabolic syndrome in patients with RA (odds ratio [OR] about 1 in both studies). [103,106] CRP levels have been associated with lipid abnormalities, [77,115] negatively correlating with high-density lipoprotein cholesterol (HDL-C) [116]. However, a direct biological link between CRP levels and metabolic syndrome in RA has yet to be established.

Conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and bDMARDs all increase lipid levels, [117−121] but TNFis improve insulin resistance and sensitivity,

[122−124] and tocilizumab does not appear to significantly affect body mass index, waist circumference, or atherogenic index [118,125]. so the overall impact of RA treatments on metabolic syndrome is, as yet, not firmly established.

Diabetes

Patients with RA are up to twice as likely to be diagnosed with diabetes mellitus (DM) than are the general population, [126−128] and the prevalence of DM in RA is about 13−20%. [6,126,129] Higher CRP levels have been seen in RA patients with type 2 diabetes (T2DM) compared with those without [126]. High CRP levels in RA have also been correlated with impaired glucose tolerance and metabolism and to insulin resistance, [130] and are significantly associated with small increased likelihood of impaired fasting glucose (OR 1.02, 95% CI 1.001−1.034, p = 0.02) [128]. Significant positive associations between the homeostatic model assessment of insulin resistance and CRP and IL-6 levels have also been seen in patients with RA. [111,113,114] However, as for metabolic syndrome in RA, no direct biological link between CRP levels and diabetes in patients with RA has yet been established.

There is evidence that treatment with DMARDs may reduce the risk for T2DM, [131−133] and reduce glycosylated haemoglobin levels (HbA1c) [134] in patients with RA. In the CORRONA registry, treatment with TNFis significantly reduced the risk for T2DM (OR 0.35, 95% CI 0.13−0.91, p = 0.03), while other bDMARDs (OR 0.44, 95% CI 0.08−2.57, p = 0.36), methotrexate (OR 0.67, 95% CI 0.44−1.02, p = 0.34), and hydroxychloroquine (OR 0.45, 95% CI 0.13−1.53, p = 0.21) numerically reduced the risk for T2DM versus patients treated with other csDMARDs [133]. In contrast, the risk for T2DM escalates with increasing doses of glucocorticoids (HR 2.33, 95% CI 1.68−3.22, p = 0.02 for patients using ≥7.5 mg glucocorticoid versus no glucocorticoid) [133]. In a retrospective analysis in Japan, HbA1c levels significantly decreased after 3 months of treatment with either TNFis or tocilizumab (p < 0.001 for both treatments) in patients with RA, including in the subgroup of patients with DM. In this analysis, tocilizumab was associated with greater reductions in HbA1c levels than were TNFis (OR 5.59, 95% CI 2.56−12.2, p < 0.001) [134]. In a post-hoc analysis of sarilumab phase III trials, patients with RA and diabetes had greater improvements in HbA1c with sarilumab 200 mg every 2 weeks (q2w) than with adalimumab 40 mg q2w (−0.43 versus −0.02 at 24 weeks) or placebo (−0.60, −0.33, and 0.18 at 24 weeks for sarilumab 200 mg, 150 mg, and placebo q2w, respectively) [135]. Given the prevalence of DM in RA, the decrease in risk for T2DM and improvements in HbA1c levels with different DMARD treatments should be considered when personalizing RA treatment.

Pulmonary disease

RA is associated with a 70−100% increased risk for COPD compared with controls, [136−139] and the prevalence of COPD among RA patients is about 4−8%. [6,137,138] COPD has been shown to increase the risk for mortality almost 3-fold in patients with RA. [140,141] High CRP levels have been associated with increased risk for COPD, [142] and higher CRP levels are seen in patients with stable COPD than controls [143,144]. As COPD exacerbations are often caused by infections, the finding that CRP levels are significantly higher in patients with acutely exacerbated versus stable COPD (p < 0.05) is not surprising [144]. In the USA NHANES survey, elevated CRP (>10 mg/L) was associated with increased risk for mortality (HR 4.45, 95% CI 1.91−10.37) in patients with COPD, [145] and a separate analysis showed that CRP ≥3 mg/L was associated with increased mortality (HR 1.61, 95% CI 1.12−2.30) [146]. CRP levels ≥3 mg/L in stable COPD are associated with poor predicted forced vital capacity and patient-reported health status [147,148].

Data on the effects of RA treatments on COPD are limited, but due to more frequent respiratory adverse events seen among patients with COPD in the ASSURE trial, the risk for COPD exacerbations with abatacept has recently been described [149]. In retrospective population-based cohort studies of patients with RA and COPD, abatacept was not associated with significantly increased risk for COPD exacerbation or respiratory adverse events compared with csDMARDs, tsDMARDs, TNFis, or other bDMARDs [150,151]. Data from RCTs for patients with RA and comorbid COPD would be valuable to further investigate the effects of DMARD treatment to determine whether reducing the generally higher CRP levels seen in patients with RA may impact positively their COPD.

The lifetime risk for patients with RA developing ILD has been reported at 6−15%, compared with 1% for the general population [152,153]. ILD may occur before the development of articular manifestations in RA [152,154,155]. A population-based study in Denmark found that 14% of ILD cases in patients with RA were diagnosed 1−5 years before RA diagnosis, and 34% within 1 year prior to and 1 year after RA diagnosis [155]. Pulmonary abnormalities compatible with ILD were present in 21/36 patients (58%) with recent onset RA (duration of joint symptoms <2 years) who were referred to a university rheumatology department [156]. The main risk factors for developing RA-ILD are smoking, older age, male sex, rheumatoid factor, and anti-cyclic citrullinated peptide antibody levels [154,157]. Of the RA-ILD subtypes, usual interstitial pneumonia (UIP) is generally the most common, followed by non-specific interstitial pneumonia (NSIP) [157,158]. RA-ILD is associated with poor prognosis, with hazard rate ratios for death 2−10 times higher in RA-ILD than in RA without ILD [155]. Patients with a UIP histological pattern have the worst prognosis, with mortality rates similar to those observed among patients with idiopathic pulmonary fibrosis [159−162].

It is uncertain if high CRP is related to progression of ILD in RA. Although higher CRP levels in patients with RA-ILD versus RA without ILD have been observed in several retrospective studies in Asia, [163−165] this pattern was not seen in an Italian retrospective study [166]. Additionally, the association of high CRP levels with risk for ILD was not significant in a multivariate analysis in Chinese patients, suggesting that CRP level may not be an independent risk factor for ILD [163].

Depression

Depression is highly prevalent in patients with RA, with a reported prevalence of 15−40%, and it is more common in patients with RA than in the general population [6,167]. Elevated CRP, TNF-α, and IL-6 levels have been noted in some studies in RA patients with depression [168,169]. Elevated CRP has been associated with higher depression scores in patients with RA [170−172]. However, the association between systemic inflammation and depressive symptoms is complicated by factors such as pain and disease activity, which may attenuate the link between CRP and depression [170−172].

The relationship between depression and treatment response in RA appears to be bidirectional. In the CARDERA RCT in patients with early RA who received methotrexate or methotrexate plus prednisolone and/or cyclosporine, patients reporting persistent depression/anxiety were significantly less likely (62−90%; $p < 0.05$) to achieve clinical remission (DAS28 <2.6) over 2 years [173]. In a large UK observational study, depressive symptoms at baseline did not predict non-response to methotrexate after 6 months of treatment [174]. Additionally, compared with RA patients without depressive symptoms, patients with depressive symptoms at bDMARD initiation were 20−40% less likely to achieve a EULAR good treatment response after 1 year [175]. Conversely, in a USA retrospective observational study, patients with RA but no depressive symptoms at baseline who responded to TNFi treatment were 20% less likely to develop depression than were non-responders (7.1% versus 9.4%; $p < 0.005$;

adjusted OR 0.80, 95% CI 0.64−0.98) [176]. Etanercept has also shown small but significant effects (7−28%) in reducing depression scores compared with methotrexate in patients with RA [177]. Analyses of patient-reported outcomes in phase III trials in RA showed improved Mental Health and Role Emotional domain scores of Short Form 36 with sarilumab, tocilizumab, and tofacitinib [178−180]. Further, in an interim analysis of the ARATA study of tocilizumab treatment in routine practice, tocilizumab improved depressive symptoms over 2 years, [181] and in the ACT-AXIS prospective observational study, tocilizumab significantly decreased depression score ($p < 0.005$). [182] Given the complex interplay of depression with RA disease activity, inflammation, and RA symptoms, poorer RA treatment outcome may be influenced, at least in part, by presence of depressive symptoms [183].

Clinical implications of CRP in the management of patients with RA

Circulating CRP level is routinely tested, as it is an inexpensive and readily available biomarker to assess systemic inflammation and clinical outcomes in RA. CRP levels can be assessed via standard or hsCRP assays, with values <10 mg/L and <1 mg/L, respectively, generally considered normal, although thresholds may differ between assays [33,184]. In RA, given the generally elevated levels of CRP due to systemic inflammation, the hsCRP assay is typically considered unnecessary. There are limitations of conventional CRP testing: for the substantial proportion of patients who have normal CRP levels while exhibiting RA disease activity or flare, [36,37] a low CRP level may provide false reassurance of reduced inflammation. Additionally, while CRP is a marker of systemic inflammation, it is not useful as an independent factor for predicting the risk for developing RA, [185,186] and it does not confirm a diagnosis of RA. In the context of comorbidities in RA, a specific CRP level/threshold is not a predictor for any particular comorbidity.

Screening for CV risk factors in patients with RA

Given the increased morbidity and mortality associated with CVD in RA compared with the age- and gender-matched population, CV risk should be assessed for all patients [192]. General CV risk calculators, such as SCORE and the Framingham risk score, may underestimate the CV risk in RA, and RA-specific calculators like EULAR multiplier and expanded CV risk prediction score (ERS-RA) do not appear to perform better than the general risk calculators [193,194]. The Reynolds risk score is the only measure that includes CRP, and it may be sensitive to the fluctuating inflammation seen in patients with RA [195]. The addition of CRP to the Framingham risk score and QRISK algorithms was not associated with significant improvement in reclassification of CV risk [196]. There is controversy about which risk calculator to use as the rates of CV events in people with RA are decreasing, but so are those of the matched population, so a gap still exists with more CV events in RA [197,198].

Effects of treatment for RA on CRP levels

Treatment of RA with DMARDs aims to reduce systemic inflammation and improve disease activity. As a measure of systemic inflammation it would be expected that CRP levels will fall in response to treatment and indeed this is observed during treatment with the different DMARD classes as shown in Supplementary Table 1. Corticosteroids and csDMARDs lead to small decreases in CRP levels [60,199−205]. TNFis decrease CRP levels, generally slightly more than csDMARDs in equivalent patient populations [41,206−209]. JAK inhibitors that target downstream signalling pathways of IL-6 and other cytokines decrease CRP levels by about 10 mg/L, with the reduction tending to be dose dependent [205,209−211]. Overall, the

most rapid, largest, and sustained decreases in CRP levels occur in response to treatment with IL-6R inhibitors, generally resulting in normalization of CRP levels [60,200,201,207,212,213]. Given the predominant role of IL-6 in stimulating CRP production, these results are not surprising.

Consistent with the decreases in CRP levels resulting from IL-6 inhibition, improvements in clinical outcome measures that include CRP have been reported. Indeed, clinical trials have demonstrated that treatment with sarilumab (MOBILITY, MONARCH, and TARGET) results in improvements in DAS28-CRP scores (up to 2.8-point decreases) and higher rates of DAS28-CRP LDA and remission (using standard thresholds of ≤3.2 [33−49%] and <2.6 [25−34%]) and of ACR20/50/70 response [61−72%/40−46%/16−25%] compared with placebo or, in MONARCH, with adalimumab [60,200,206]. Similar levels of efficacy have been seen with tocilizumab in the BREVACTA and SUMMACTA studies [204,214]. Higher rates of SDAI remission with tocilizumab than with TNFi treatment have also been seen in a real-world observational study (SDAI ≤3.3 32% versus 22%, $p < 0.05$ at Week 52) [207]. The JAK inhibitor upadacitinib demonstrated superiority to adalimumab for DAS28-CRP LDA and remission in a phase III trial of patients with RA and an inadequate response to methotrexate [215]. Importantly, RA drugs that influence CRP levels have also been shown to improve RA disease activity using scores that do not include a CRP component, indicating their effects on disease activity in RA extend beyond those driven by systemic inflammation. For example, in the most recent sarilumab phase III trial (MONARCH), the primary efficacy endpoint was change in DAS28-ESR at 24 weeks, and sarilumab produced significantly greater improvement than adalimumab (−3.28 versus −2.20, respectively; $p < 0.0001$) [206].

Subgroup analyses of IL-6R inhibitor RCTs are suggestive of how clinical outcomes may be associated with CRP. Evaluation of baseline CRP subgroups in MOBILITY and MONARCH showed that the treatment effect of sarilumab was greater in the group with baseline CRP >15 mg/L both for radiographic progression (mean modified total Sharp score change at Week 52, sarilumab 0.90−1.00 versus placebo 4.25) [216] and for greater improvement versus adalimumab even when using the DAS28-ESR score [217]. In MOBILITY, patients receiving sarilumab who achieved DAS28-CRP <3.2 versus those who did not exhibited a slightly greater percentage decrease from baseline in CRP after 24 weeks (−97% versus −90%, nominal $p < 0.01$) [218]. Similar trends were seen in TARGET for ACR50 responders versus non-responders [201]. However, despite the link between IL-6 inhibition and CRP levels, CRP does not appear to be a consistent predictive biomarker for response to tocilizumab treatment. An analysis of BREVACTA and SUMMACTA demonstrated that baseline CRP levels were not predictive of clinical outcomes after tocilizumab treatment [213]. In contrast, the RADIATE study demonstrated that tocilizumab treatment led to a significant decrease in a matrix metalloproteinases-degraded fragment of CRP, reducing tissue inflammation, with the decrease correlating with improvements in pain, functional status, DAS28, and the likelihood of ACR20/50 response [219]. Overall, further investigation of the relationship of baseline and change in CRP levels with clinical outcomes after IL-6 inhibition is needed to understand how they are linked.

There is extremely limited evidence on whether changes in CRP levels resulting from DMARD treatment may also affect the risk for developing or exacerbating common comorbidities. In a single-centre longitudinal cohort study of 90 patients with RA who were receiving DMARDs and experienced reductions of CRP >10 mg/L, increases in low-density lipoprotein cholesterol levels and improvements in HDL-C efflux capacity suggested that reducing systemic inflammation improved the lipid profile and potentially reduced CV risk [115]. However, the relationship between reducing CRP levels and a potential reduction in CV risk remains to be elucidated. More research is needed to investigate specific associations between reductions in CRP levels resulting from DMARD treatment and the impact on comorbidities.

In conclusion, CRP is a valuable marker and regulator of systemic inflammation in RA that also appears to play a direct role in bone destruction and radiographic progression. CRP has also been implicated in the aetiology of common comorbidities associated with RA. Reducing CRP levels with RA treatment may contribute to reductions in disease activity, although beneficial effects of RA treatment seem to occur irrespective of CRP values.

Contributions

The authors contributed equally to researching data for the article, substantial discussion of content and writing, reviewing and editing the manuscript before submission.

Declaration of Competing Interest

Role of the funding source

Supplementary materials

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References

[1] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205–19. doi: 10.1056/NEJMra1004965.

[2] Bombardier C, et al. The relationship between joint damage and functional disability in rheumatoid arthritis: a systematic review. Ann Rheum Dis 2012;71:836–44. doi: 10.1136/annrheumdis-2011-200343.

[3] Buttgereit F, Smolen JS, Coogan AN, Cajochen C. Clocking in: chronobiology in rheumatoid arthritis. Nat Rev Rheumatol 2015;11:349–56. doi: 10.1038/nrrheum.2015.31.

[4] Cutolo M, Kitas GD, van Riel PL. Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. Semin Arthritis Rheum 2014;43:479–88. doi: 10.1016/j.semarthrit.2013.08.004.

[5] Strand V, Singh JA. Newer biological agents in rheumatoid arthritis: impact on health-related quality of life and productivity. Drugs 2010;70:121–45. doi: 10.2165/11531980-000000000-00000.

[6] Dougados M, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis 2014;73:62–8. doi: 10.1136/annrheumdis-2013-204223.

[7] Radner H, Yoshida K, Smolen JS, Solomon DH. Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity. Nat Rev Rheumatol 2014;10:252–6. doi: 10.1038/nrrheum.2013.212.

[8] Ranganath VK, et al. Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. Rheumatology 2013;52:1809–17. doi: 10.1093/rheumatology/ket224.

[9] Peters MJL, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325–31. doi: 10.1136/ard.2009.113696.

[10] Solomon DH, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006;65:1608–12. doi: 10.1136/ard.2005.050377.

[11] Symmons DPM, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol 2011;7:399–408. doi: 10.1038/nrrheum.2011.75.

[12] Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. Immunity 2017;46:183–96. doi: 10.1016/j.immuni.2017.02.006.

[13] Ridgley LA, Anderson AE, Pratt AG. What are the dominant cytokines in early rheumatoid arthritis? Curr Opin Rheumatol 2018;30:207–14. doi: 10.1097/BOR.0000000000000470.

[14] Castell JV, et al. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. FEBS Lett 1989;242:237–9. doi: 10.1016/0014-5793(89)80476-4.

[15] Choy E, Rose-John S. Interleukin-6 as a multifunctional regulator: inflammation, immune response, and fibrosis. J Scleroderma Relat Disord 2017;2:S1–5. doi: 10.5301/jsrd.5000265.

[16] Jones SA, et al. Interleukin 6: the biology behind the therapy. Consid Med 2018;2:2–6.

[17] Ansar W, Ghosh S. C-reactive protein and the biology of disease. Immunol Res 2013;56:131–42. doi: 10.1007/s12026-013-8384-0.

[18] Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018;9:754. doi: 10.3389/fimmu.2018.00754.

[19] Chung S-J, Kwon Y-J, Park M-C, Park Y-B, Lee S-K. The correlation between increased serum concentrations of interleukin-6 family cytokines and disease activity in rheumatoid arthritis patients. Yonsei Med J 2011;52:113–20. doi: 10.3349/ymj.2011.52.1.113.

[20] Kim K-W, Kim B-M, Moon H-W, Lee S-H, Kim H-R. Role of C-reactive protein in osteoclastogenesis in rheumatoid arthritis. Arthritis Res Ther 2015;17:41. doi: 10.1186/s13075-015-0563-z.

[21] Meyer PWA, et al. Circulating cytokine profiles and their relationships with autoantibodies, acute phase reactants, and disease activity in patients with rheumatoid arthritis. Mediators Inflamm 2010;2010:158514. doi: 10.1155/2010/158514.

[22] Milman N, Karsh J, Booth RA. Correlation of a multi-cytokine panel with clinical disease activity in patients with rheumatoid arthritis. Clin Biochem 2010;43:1309–14. doi: 10.1016/j.clinbiochem.2010.07.012.

[23] Wang J, et al. IL-6 pathway-driven investigation of response to IL-6 receptor inhibition in rheumatoid arthritis. BMJ Open 2013;3:e003199. doi: 10.1136/bmjopen-2013-003199.

[24] Eisenhardt SU, Thiele JR, Bannasch H, Stark GB, Peter K. C-reactive protein: how conformational changes influence inflammatory properties. Cell Cycle 2009;8:3885–92. doi: 10.4161/cc.8.23.10068.

[25] Thiele JR, et al. Targeting C-reactive protein in inflammatory disease by preventing conformational changes. Mediators Inflamm 2015;2015:372432. doi: 10.1155/2015/372432.

[26] McFadyen JD, et al. Dissociation of C-reactive protein localizes and amplifies inflammation: evidence for a direct biological role of c-reactive protein and its conformational changes. Front Immunol 2018;9:1351. doi: 10.3389/fimmu.2018.01351.

[27] Newling M, et al. C-Reactive protein promotes inflammation through FcγR-Induced glycolytic reprogramming of human macrophages. J Immunol 2019;203:225–35. doi: 10.4049/jimmunol.1900172.

[28] Salazar J, et al. C-reactive protein: an in-depth look into structure, function, and regulation. Int Sch Res Notices 2014;2014:653045. doi: 10.1155/2014/653045.

[29] Lu J, et al. Structural recognition and functional activation of FcgammaR by innate pentraxins. Nature 2008;456:989–92. doi: 10.1038/nature07468.

[30] Urman A, Taklalsingh N, Sorrento C, McFarlane IM. Inflammation beyond the joints: rheumatoid arthritis and cardiovascular disease. Scifed J Cardiol 2018;2.

[31] Devaraj S, Venugopal S, Jialal I. Native pentameric C-reactive protein displays more potent pro-atherogenic activities in human aortic endothelial cells than modified C-reactive protein. Atherosclerosis 2006;184:48–52. doi: 10.1016/j.atherosclerosis.2005.03.031.

[32] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805–12. doi: 10.1172/JCI18921.

[33] FDA. Review Criteria for Assessment of C Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays - Guidance for Industry and FDA Staff, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/review-criteria-assessment-c-reactive-protein-crp-high-sensitivity-c-reactive-protein-hscrp-and>(2005).

[34] Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obes Rev 2013;14:232–44. doi: 10.1111/obr.12003.

[35] Kilcher G, et al. Rheumatoid arthritis patients treated in trial and real world settings: comparison of randomized trials with registries. Rheumatology 2018;57:354–69. doi: 10.1093/rheumatology/kex394.

[36] Kay J, et al. Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels contribute separately to predicting outcome at one year. Arthritis Res Ther 2014;16:R40. doi: 10.1186/ar4469.

[37] Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%–45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. J Rheumatol 2009;36:1387–90. doi: 10.3899/jrheum.080770.

[38] Ammitzbøll CG, et al. CRP genotype and haplotype associations with serum C-reactive protein level and DAS28 in untreated early rheumatoid arthritis patients. Arthritis Res Ther 2014;16:475. doi: 10.1186/s13075-014-0475-3.

[39] Danila MI, et al. The role of genetic variants in CRP in radiographic severity in African Americans with early and established rheumatoid arthritis. Genes Immun 2015;16:446–51. doi: 10.1038/gene.2015.24.

[40] Rhodes B, et al. A genetic association study of serum acute-phase C-reactive protein levels in rheumatoid arthritis: implications for clinical interpretation. PLoS Med 2010;7:e1000341. doi: 10.1371/journal.pmed.1000341.

[41] Plant D, et al. Correlation of C-reactive protein haplotypes with serum C-reactive protein level and response to anti-tumor necrosis factor therapy in UK rheumatoid arthritis patients: results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. Arthritis Res Ther 2012;14:R214. doi: 10.1186/ar4052.

[42] Bärebring L, Winkvist A, Gjertsson I, Lindqvist HM. Poor dietary quality is associated with increased inflammation in swedish patients with rheumatoid arthritis. Nutrients 2018;10:1535. doi: 10.3390/nu10101535.

[43] Giles JT, et al. Association of body fat with C-reactive protein in rheumatoid arthritis. Arthritis Rheum 2008;58:2632–41. doi: 10.1002/art.23766.

[44] Kàss AS, Lea TE, Torjesen PA, Gulseth HC, Fòrre ØT. The association of luteinizing hormone and follicle-stimulating hormone with cytokines and markers of disease activity in rheumatoid arthritis: a case-control study. Scand J Rheumatol 2010;39:109–17. doi: 10.3109/03009740903270607.

[45] Veldhuijzen van Zanten JJ, Ring C, Carroll D, Kitas GD. Increased C reactive protein in response to acute stress in patients with rheumatoid arthritis. Ann Rheum Dis 2005;64:1299–304. doi: 10.1136/ard.2004.032151.

[46] Orr CK, et al. The utility and limitations of CRP, ESR and DAS28-CRP in appraising disease activity in rheumatoid arthritis. Front Med 2018;5:185. doi: 10.3389/fmed.2018.00185.

[47] Cho I-J, et al. Effects of C-reactive protein on bone cells. Life Sci 2016;145:1–8. doi: 10.1016/j.lfs.2015.12.021.

[48] Jia Z-K, et al. Monomeric C-reactive protein binds and neutralizes receptor activator of NF-κB ligand-induced osteoclast differentiation. Front Immunol 2018;9:234. doi: 10.3389/fimmu.2018.00234.

[49] Fukui S, et al. M1 and M2 monocytes in rheumatoid arthritis: a contribution of imbalance of M1/M2 monocytes to osteoclastogenesis. Front Immunol 2018;8:1958. doi: 10.3389/fimmu.2017.01958.

[50] Cylwik B, Chrostek L, Gindzienska-Sieskiewicz E, Sierakowski S, Szmitkowski M. Relationship between serum acute-phase proteins and high disease activity in patients with rheumatoid arthritis. Adv Med Sci 2010;55:80–5. doi: 10.2478/v10039-010-0006-7.

[51] Yildirim K, et al. Associations between acute phase reactant levels and disease activity score (DAS28) in patients with rheumatoid arthritis. Ann Clin Lab Sci 2004;34:423–6.

[52] Dessein PH, Joffe BI, Stanwix AE. High sensitivity C-reactive protein as a disease activity marker in rheumatoid arthritis. J Rheumatol 2004;31:1095–7.

[53] Jansen LM, van Schaardenburg D, van Der Horst-Bruinsma IE, Bezemer PD, Dijkmans BA. Predictors of functional status in patients with early rheumatoid arthritis. Ann Rheum Dis 2000;59:223–6. doi: 10.1136/ard.59.3.223.

[54] Keenan RT, Swearingen CJ, Yazici Y. Erythrocyte sedimentation rate and C-reactive protein levels are poorly correlated with clinical measures of disease activity in rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis patients. Clin Exp Rheumatol 2008;26:814–9.

[55] Madsen SG, Danneskiold-Samsøe B, Stockmarr A, Bartels EM. Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review. Scand J Rheumatol 2016;45:255–61. doi: 10.3109/03009742.2015.1095943.

[56] Sarzi-Puttini P, et al. Correlation of the score for subjective pain with physical disability, clinical and radiographic scores in recent onset rheumatoid arthritis. BMC Musculoskelet Disord 2002;3:18. doi: 10.1186/1471-2474-3-18.

[57] England BR, et al. 2019 Update of the American College of Rheumatology recommended rheumatoid arthritis disease activity measures. Arthritis Care Res 2019;71:1540–55. doi: 10.1002/acr.24042.

[58] Felson DT, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13. doi: 10.1136/ard.2011.149765.

[59] Wells G, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68:954–60. doi: 10.1136/ard.2007.084459.

[60] Genovese MC, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. Arthritis Rheumatol 2015;67:1424–37. doi: 10.1002/art.39093.

[61] Ally MMTM, et al. Serum matrix metalloproteinase-3 in comparison with acute phase proteins as a marker of disease activity and radiographic damage in early rheumatoid arthritis. Mediators Inflamm 2013;2013:183653. doi: 10.1155/2013/183653.

[62] Curtis JR, et al. Predicting risk for radiographic damage in rheumatoid arthritis: comparative analysis of the multi-biomarker disease activity score and conventional measures of disease activity in multiple studies. Curr Med Res Opin 2019:1−11. doi: 10.1080/03007995.2019.1585064.

[63] Emery P, Gabay C, Kraan M, Gomez-Reino J. Evidence-based review of biologic markers as indicators of disease progression and remission in rheumatoid arthritis. Rheumatol Int 2007;27:793−806. doi: 10.1007/s00296-007-0357-y.

[64] Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BA. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:924−7. doi: 10.1136/ard.60.10.924.

[65] Navarro-Compán V, et al. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology 2015;54:994−1007. doi: 10.1093/rheumatology/keu413.

[66] Vanier A, et al. An updated matrix to predict rapid radiographic progression of early rheumatoid arthritis patients: pooled analyses from several databases. Rheumatology 2019:kez542. doi: 10.1093/rheumatology/kez542.

[67] Bay-Jensen AC, et al. Tissue metabolite of type I collagen, C1M, and CRP predicts structural progression of rheumatoid arthritis. BMC Rheumatol 2019;3:3. doi: 10.1186/s41927-019-0052-0.

[68] Yeh J-C, et al. Non-hepatic alkaline phosphatase, hs-CRP and progression of vertebral fracture in patients with rheumatoid arthritis: a population-based longitudinal study. J Clin Med 2018;7:439. doi: 10.3390/jcm7110439.

[69] Agca R, et al. Cardiovascular event risk in rheumatoid arthritis compared with type 2 Diabetes: a 15-year longitudinal study. J Rheumatol 2019:180726. doi: 10.3899/jrheum.180726.

[70] Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71:1524−9. doi: 10.1136/annrheumdis-2011-200726.

[71] Ogdie A, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis 2015;74:326−32. doi: 10.1136/annrheumdis-2014-205675.

[72] Pujades-Rodriguez M, et al. Rheumatoid arthritis and incidence of twelve initial presentations of cardiovascular disease: a population record-linkage cohort study in England. PLoS One 2016;11:e0151245. doi: 10.1371/journal.pone.0151245.

[73] Cooksey R, et al. Cardiovascular risk factors predicting cardiac events are different in patients with rheumatoid arthritis, psoriatic arthritis, and psoriasis. Semin Arthritis Rheum 2018;48:367−73. doi: 10.1016/j.semarthrit.2018.03.005.

[74] England BR, Thiele GM, Anderson DR, Mikuls TR. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. BMJ 2018;361:k1036. doi: 10.1136/bmj.k1036.

[75] Fransen J, Kazemi-Bajestani SMR, Bredie SJH, Popa CD. Rheumatoid Arthritis disadvantages younger patients for cardiovascular diseases: a meta-analysis. PLoS One 2016;11:e0157360. doi: 10.1371/journal.pone.0157360.

[76] Aday AW, Ridker PM. Targeting residual inflammatory risk: a shifting paradigm for atherosclerotic disease. Front Cardiovasc Med 2019;6:16. doi: 10.3389/fcvm.2019.00016.

[77] Choy E, Ganeshalingam K, Semb AG, Szekanecz Z, Nurmohamed M. Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. Rheumatology 2014;53:2143−54. doi: 10.1093/rheumatology/keu224.

[78] Danesh J, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387−97. doi: 10.1056/NEJMoa032804.

[79] Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res 2016;118:145−56. doi: 10.1161/CIRCRESAHA.115.306656.

[80] Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:483−95. doi: 10.7326/0003-4819-151-7-200910060-00009.

[81] Emerging Risk Factors Collaboration. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 2012;367:1310−20. doi: 10.1056/NEJMoa1107477.

[82] Badimon L, et al. C-reactive protein in atherothrombosis and angiogenesis. Front Immunol 2018;9:430. doi: 10.3389/fimmu.2018.00430.

[83] Attar SM. Hyperlipidemia in rheumatoid arthritis patients in Saudi Arabia. Correlation with C-reactive protein levels and disease activity. Saudi Med J 2015;36:685−91. doi: 10.15537/smj.2015.6.10557.

[84] Park Y-J, Cho C-S, Emery P, Kim W-U. LDL cholesterolemia as a novel risk factor for radiographic progression of rheumatoid arthritis: a single-center prospective study. PLoS ONE 2013;8:e68975. doi: 10.1371/journal.pone.0068975.

[85] Zhang J, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 2014;73:1301−8. doi: 10.1136/annrheumdis-2013-204715.

[86] Myasoedova E, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70:482−7. doi: 10.1136/ard.2010.135871.

[87] Navarro-Millán I, et al. Association of hyperlipidaemia, inflammation and serological status and coronary heart disease among patients with rheumatoid arthritis: data from the National Veterans Health Administration. Ann Rheum Dis 2016;75:341−7. doi: 10.1136/annrheumdis-2013-204987.

[88] Gonzalez-Gay MA, et al. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis Rheum 2007;57:125−32. doi: 10.1002/art.22482.

[89] Goodson NJ, et al. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. Arthritis Rheum 2005;52:2293−9. doi: 10.1002/art.21204.

[90] Ambrosino P, et al. Subclinical atherosclerosis in patients with rheumatoid arthritis. A meta-analysis of literature studies. Thromb Haemost 2015;113:916−30. doi: 10.1160/TH14-11-0921.

[91] Giles JT, et al. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. Arthritis Rheum 2011;63:3216−25. doi: 10.1002/art.30542.

[92] Gonzalez-Gay MA, et al. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. J Rheumatol 2005;32:1219−23.

[93] Ruscitti P, et al. Subclinical and clinical atherosclerosis in rheumatoid arthritis: results from the 3-year, multicentre, prospective, observational GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale) study. Arthritis Res Ther 2019;21:204. doi: 10.1186/s13075-019-1975-y.

[94] Vázquez-Del Mercado M, et al. Serum levels of anticyclic citrullinated peptide antibodies, interleukin-6, tumor necrosis factor-α, and C-reactive protein are associated with increased carotid intima-media thickness: a cross-sectional analysis of a cohort of rheumatoid arthritis patients without cardiovascular risk factors. Biomed Res Int 2015;2015:342649. doi: 10.1155/2015/342649.

[95] Solomon DH, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol 2015;67:1449−55. doi: 10.1002/art.39098.

[96] Roubille C, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:480−9. doi: 10.1136/annrheumdis-2014-206624.

[97] Kang EH, et al. Comparative cardiovascular risk of abatacept and tumor necrosis factor inhibitors in patients with rheumatoid arthritis with and without diabetes mellitus: a multidatabase cohort study. J Am Heart Assoc 2018;7:e007393. doi: 10.1161/JAHA.117.007393.

[98] Rao VU, et al. An evaluation of risk factors for major adverse cardiovascular events during tocilizumab therapy. Arthritis Rheumatol 2015;67:372−80. doi: 10.1002/art.38920.

[99] Giles JT, et al. Cardiovascular safety of tocilizumab versus etanercept in rheumatoid arthritis: a randomized controlled trial. Arthritis Rheumatol 2020;72:31−40. doi: 10.1002/art.41095.

[100] Fleischmann R, et al. Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up. Rheumatology 2020;59:292−302. doi: 10.1093/rheumatology/kez265.

[101] Charles-Schoeman C, et al. Risk factors for major adverse cardiovascular events in phase III and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol 2019;71:1450−9. doi: 10.1002/art.40911.

[102] Taylor PC, et al. Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. Arthritis Rheumatol 2019;71:1042−55. doi: 10.1002/art.40841.

[103] Crowson CS, et al. Increased prevalence of metabolic syndrome associated with rheumatoid arthritis in patients without clinical cardiovascular disease. J Rheumatol 2011;38:29−35. doi: 10.3899/jrheum.100346.

[104] da Cunha VR, et al. Metabolic syndrome prevalence is increased in rheumatoid arthritis patients and is associated with disease activity. Scand J Rheumatol 2012;41:186−91. doi: 10.3109/03009742.2011.626443.

[105] Hallajzadeh J, et al. Metabolic syndrome and its components among rheumatoid arthritis patients: a comprehensive updated systematic review and meta-analysis. PLoS ONE 2017;12:e0170361. doi: 10.1371/journal.pone.0170361.

[106] Kuriya B, et al. Prevalence and characteristics of metabolic syndrome differ in men and women with early rheumatoid arthritis. ACR Open Rheumatol 2019;1:535−41. doi: 10.1002/acr2.11075.

[107] Pandey PK, Swami A, Biswas TK, Thakuria R. Prevalence of metabolic syndrome in treatment naïve rheumatoid arthritis and correlation with disease parameters. Arch Rheumatol 2016;32:46−52. doi: 10.5606/ArchRheumatol.2017.5949.

[108] Šalamon L, et al. Differences in the prevalence and characteristics of metabolic syndrome in rheumatoid arthritis and osteoarthritis: a multicentric study. Rheumatol Int 2015;35:2047−57. doi: 10.1007/s00296-015-3307-0.

[109] Giles JT, et al. Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. Arthritis Rheum 2010;62:3173−82. doi: 10.1002/art.27629.

[110] Bellan M, et al. Inflammatory markers predict insulin sensitivity in active rheumatoid arthritis but not in psoriatic arthritis. Reumatismo 2018;70:232−40. doi: 10.4081/reumatismo.2018.1061.

[111] Chung CP, et al. Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum 2008;58:2105−12. doi: 10.1002/art.23600.

[112] Dessein PH, Stanwix AE, Joffe BI. Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. Arthritis Res 2002;4:R5. doi: 10.1186/ar428.

[113] Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum 2006;54:2765−75. doi: 10.1002/art.22053.

[114] Giles JT, et al. Insulin resistance in rheumatoid arthritis: disease-related indicators and associations with the presence and progression of subclinical atherosclerosis. Arthritis Rheumatol 2015;67:626−36. doi: 10.1002/art.38986.

[115] Liao KP, et al. The association between reduction in inflammation and changes in lipoprotein levels and HDL cholesterol efflux capacity in rheumatoid arthritis. J Am Heart Assoc 2015;4:e001588. doi: 10.1161/JAHA.114.001588.

[116] Gan L, He Y, Liu L, Ou Q, Lin J. Association of serum lipids with autoantibodies and inflammatory markers in rheumatoid arthritis patients. Clin Chim Acta 2018;486:282−90. doi: 10.1016/j.cca.2018.08.028.

[117] Charles-Schoeman C, et al. Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. Semin Arthritis Rheum 2016;46:71−80. doi: 10.1016/j.semarthrit.2016.03.004.

[118] Hoffman E, et al. Effects of tocilizumab, an anti-interleukin-6 receptor antibody, on serum lipid and adipokine levels in patients with rheumatoid arthritis. Int J Mol Sci 2019;20:4633. doi: 10.3390/ijms20184633.

[119] McInnes IB, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. Ann Rheum Dis 2015;74:694−702. doi: 10.1136/annrheumdis-2013-204345.

[120] Qiu C, et al. Baricitinib induces LDL-C and HDL-C increases in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Lipids Health Dis 2019;18:54. doi: 10.1186/s12944-019-0994-7.

[121] Taylor PC, et al. Lipid profile and effect of statin treatment in pooled phase II and phase III baricitinib studies. Ann Rheum Dis 2018;77:988−95. doi: 10.1136/annrheumdis-2017-212461.

[122] Leporini C, et al. Insulin-sensiting effects of tumor necrosis factor alpha inhibitors in rheumatoid arthritis: a systematic review and meta-analysis. Rev Recent Clin Trials 2018;13:184−91. doi: 10.2174/1574887113666180314100340.

[123] Stagakis I, et al. Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. Arthritis Res Ther 2012;14:R141. doi: 10.1186/ar3874.

[124] Stavropoulos-Kalinoglou A, et al. Anti-tumour necrosis factor alpha therapy improves insulin sensitivity in normal-weight but not in obese patients with rheumatoid arthritis. Arthritis Res Ther 2012;14:R160. doi: 10.1186/ar3900.

[125] Tournadre A, et al. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. J Cachexia Sarcopenia Muscle 2017;8:639−46. doi: 10.1002/jcsm.12189.

[126] Emamifar A, Levin K, Jensen Hansen IM. Patients with newly diagnosed rheumatoid arthritis are at increased risk of diabetes mellitus: an observational cohort study. Acta Reumatol Port 2017;42:310−7.

[127] Jiang P, Li H, Li X. Diabetes mellitus risk factors in rheumatoid arthritis: a systematic review and meta-analysis. Clin Exp Rheumatol 2015;33:115−21.

[128] Ruscitti P, et al. Prevalence of type 2 diabetes and impaired fasting glucose in patients affected by rheumatoid arthritis: results from a cross-sectional study. Medicine 2017;96:e7896. doi: 10.1097/MD.0000000000007896.

[129] Albrecht K, Luque Ramos A, Hoffmann F, Redeker I, Zink A. High prevalence of diabetes in patients with rheumatoid arthritis: results from a questionnaire survey linked to claims data. Rheumatology 2018;57:329−36. doi: 10.1093/rheumatology/kex414.

[130] Ursini F, et al. Prevalence of undiagnosed diabetes in rheumatoid arthritis: an OGTT study. Medicine 2016;95:e2552. doi: 10.1097/MD.0000000000002552.

[131] Ozen G, et al. Risk of diabetes mellitus associated with disease-modifying antirheumatic drugs and statins in rheumatoid arthritis. Ann Rheum Dis 2017;76:848−54. doi: 10.1136/annrheumdis-2016-209954.

[132] Solomon DH, et al. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA 2011;305:2525−31. doi: 10.1001/jama.2011.878.

[133] Lillegraven S, et al. Immunosuppressive treatment and the risk of diabetes in rheumatoid arthritis. PLoS One 2019;14:e0210459. doi: 10.1371/journal.pone.0210459.

[134] Otsuka Y, et al. Effects of tumor necrosis factor inhibitors and tocilizumab on the glycosylated hemoglobin levels in patients with rheumatoid arthritis; an observational study. PLoS ONE 2018;13:e0196368. doi: 10.1371/journal.pone.0196368.

[135] Burmester GR, et al. Effect of sarilumab on glycosylated hemoglobin in patients with rheumatoid arthritis and diabetes. Rheumatology 2019;58 EULAR 2019 abstract 2054 − kez2106. 2053.

[136] Gergianaki I, Tsiligianni I. Chronic obstructive pulmonary disease and rheumatic diseases: a systematic review on a neglected comorbidity. J Comorb 2019;9 2235042X18820209-12235042X18820209. doi: 10.1177/2235042X18820209.

[137] Ma Y, et al. Chronic obstructive pulmonary disease in rheumatoid arthritis: a systematic review and meta-analysis. Respir Res 2019;20:144. doi: 10.1186/s12931-019-1123-x.

[138] Sparks JA, et al. Rheumatoid arthritis and risk of chronic obstructive pulmonary disease or asthma among women: a marginal structural model analysis in the Nurses' Health Study. Semin Arthritis Rheum 2018;47:639−48. doi: 10.1016/j.semarthrit.2017.09.005.

[139] Ungprasert P, Srivali N, Cheungpasitporn W, Davis Iii JM. Risk of incident chronic obstructive pulmonary disease in patients with rheumatoid arthritis: a systematic review and meta-analysis. Joint Bone Spine 2016;83:290−4. doi: 10.1016/j.jbspin.2015.05.016.

[140] Hyldgaard C, et al. Increased mortality among patients with rheumatoid arthritis and COPD: a population-based study. Respir Med 2018;140:101−7. doi: 10.1016/j.rmed.2018.06.010.

[141] Nikiphorou E, et al. Prognostic value of comorbidity indices and lung diseases in early rheumatoid arthritis: a UK population-based study. Rheumatology 2019: kez409. doi: 10.1093/rheumatology/kez409.

[142] Bellou V, Belbasis L, Konstantinidis AK, Evangelou E. Elucidating the risk factors for chronic obstructive pulmonary disease: an umbrella review of meta-analyses. Int J Tuberc Lung Dis 2019;23:58−66. doi: 10.5588/ijtld.18.0228.

[143] Karadag F, Kirdar S, Karul AB, Ceylan E. The value of C-reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease. Eur J Intern Med 2008;19:104−8. doi: 10.1016/j.ejim.2007.04.026.

[144] Lin T-L, et al. Correlations between serum amyloid A, C-reactive protein and clinical indices of patients with acutely exacerbated chronic obstructive pulmonary disease. J Clin Lab Anal 2019;33:e22831. doi: 10.1002/jcla.22831.

[145] Mendy A, Forno E, Niyonsenga T, Gasana J. Blood biomarkers as predictors of long-term mortality in COPD. Clin Respir J 2018;12:1891−9. doi: 10.1111/crj.12752.

[146] Leuzzi G, et al. C-reactive protein level predicts mortality in COPD: a systematic review and meta-analysis. Eur Respir Rev 2017;26:160070. doi: 10.1183/16000617.0070-2016.

[147] Kang HK, et al. COPD assessment test score and serum C-reactive protein levels in stable COPD patients. Int J Chron Obstruct Pulmon Dis 2016;11:3137−43. doi: 10.2147/COPD.S118153.

[148] Silva DR, Gazzana MB, Knorst MM. C-reactive protein levels in stable COPD patients: a case-control study. Int J Chron Obstruct Pulmon Dis 2015;10:1719−25. doi: 10.2147/COPD.S87015.

[149] Weinblatt M, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum 2006;54:2807−16. doi: 10.1002/art.22070.

[150] Hudson M, et al. Comparative safety of biologic versus conventional synthetic DMARDs in rheumatoid arthritis with COPD: a real-world population study. Rheumatology 2019:kez359. doi: 10.1093/rheumatology/kez359.

[151] Kang, E.H. et al. Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: a cohort study. Semin Arthritis Rheu, 2020;50:401−8. doi:10.1016/j.semarthrit.2019.11.010.

[152] Bendstrup E, Møller J, Kronborg-White S, Prior TS, Hyldgaard C. Interstitial lung disease in rheumatoid arthritis remains a challenge for clinicians. J Clin Med 2019;8:2038. doi: 10.3390/jcm8122038.

[153] Bongartz T, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62:1583−91. doi: 10.1002/art.27405.

[154] Doyle TJ, et al. Detection of rheumatoid arthritis-interstitial lung disease is enhanced by serum biomarkers. Am J Respir Crit Care Med 2015;191:1403−12. doi: 10.1164/rccm.201411-1950OC.

[155] Hyldgaard C, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis 2017;76:1700−6. doi: 10.1136/annrheumdis-2017-211138.

[156] Gabbay E, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997;156:528−35. doi: 10.1164/ajrccm.156.2.9609016.

[157] Kelly CA, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics - a large multicentre UK study. Rheumatology 2014;53:1676−82. doi: 10.1093/rheumatology/keu165.

[158] Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology 2017;56:344−50. doi: 10.1093/rheumatology/kew391.

[159] Solomon JJ, Brown KK. Rheumatoid arthritis-associated interstitial lung disease. Open Access Rheumatol 2012;4:21−31. doi: 10.2147/OARRR.S14723.

[160] Solomon JJ, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016;47:588−96. doi: 10.1183/13993003.00357-2015.

[161] Solomon JJ, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Respir Med 2013;107:1247−52. doi: 10.1016/j.rmed.2013.05.002.

[162] Yunt ZX, et al. High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: relationship to survival. Respir Med 2017;126:100−4. doi: 10.1016/j.rmed.2017.03.027.

[163] Wang J-X, Du C-G. A retrospective study of clinical characteristics of interstitial lung disease associated with rheumatoid arthritis in Chinese patients. Med Sci Monit 2015;21:708−15. doi: 10.12659/MSM.890880.

[164] Yang JA, et al. Clinical characteristics associated with occurrence and poor prognosis of interstitial lung disease in rheumatoid arthritis. Korean J Intern Med 2019;34:434−41. doi: 10.3904/kjim.2016.349.

[165] Zhang Y, Li H, Wu N, Dong X, Zheng Y. Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol 2017;36:817−23. doi: 10.1007/s10067-017-3561-5.

[166] Salaffi F, Carotti M, Di Carlo M, Tardella M, Giovagnoni A. High-resolution computed tomography of the lung in patients with rheumatoid arthritis: prevalence of interstitial lung disease involvement and determinants of abnormalities. Medicine 2019;98:e17088. doi: 10.1097/MD.0000000000017088.

[167] Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology 2013;52:2136−48. doi: 10.1093/rheumatology/ket169.

[168] Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimaki M. Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive

protein in patients with major depressive disorder. Brain Behav Immun 2015;49:206–15. doi: 10.1016/j.bbi.2015.06.001.

[169] Li YC, Chou YC, Chen HC, Lu CC, Chang DM. Interleukin-6 and interleukin-17 are related to depression in patients with rheumatoid arthritis. Int J Rheum Dis 2019;22:980–5. doi: 10.1111/1756-185X.13529.

[170] Low CA, et al. Association between C-reactive protein and depressive symptoms in women with rheumatoid arthritis. Biol Psychol 2009;81:131–4. doi: 10.1016/j.biopsycho.2009.02.003.

[171] Kojima M, et al. Depression, inflammation, and pain in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:1018–24. doi: 10.1002/art.24647.

[172] Figueiredo-Braga M, et al. Influence of biological therapeutics, cytokines, and disease activity on depression in rheumatoid arthritis. J Immunol Res 2018;2018:5954897. doi: 10.1155/2018/5954897.

[173] Matcham F, Norton S, Scott DL, Steer S, Hotopf M. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. Rheumatology 2016;55:268–78. doi: 10.1093/rheumatology/kev306.

[174] Sergeant JC, et al. Prediction of primary non-response to methotrexate therapy using demographic, clinical and psychosocial variables: results from the UK Rheumatoid Arthritis Medication Study (RAMS). Arthritis Res Ther 2018;20:147. doi: 10.1186/s13075-018-1645-5.

[175] Matcham F, et al. The relationship between depression and biologic treatment response in rheumatoid arthritis: an analysis of the British Society for Rheumatology Biologics Register. Rheumatology 2018;57:835–43. doi: 10.1093/rheumatology/kex528.

[176] Deb A, et al. Tumor necrosis factor inhibitor therapy and the risk for depression among working-age adults with rheumatoid arthritis. Am Health Drug Benefits 2019;12:30–8.

[177] Abbott R, et al. Tumour necrosis factor-alpha inhibitor therapy in chronic physical illness: a systematic review and meta-analysis of the effect on depression and anxiety. J Psychosom Res 2015;79:175–84. doi: 10.1016/j.jpsychores.2015.04.008.

[178] Strand V, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. Rheumatology 2016;55:1031–41. doi: 10.1093/rheumatology/kev442.

[179] Strand V, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. Arthritis Res Ther 2016;18:198. doi: 10.1186/s13075-016-1096-9.

[180] Strand V, et al. Impact of tocilizumab monotherapy on patient-reported outcomes in patients with rheumatoid arthritis from two randomised controlled trials. RMD Open 2017;3:e000496. doi: 10.1136/rmdopen-2017-000496.

[181] Behrens F, et al. Tocilizumab s.c. – improvement of the depressiveness, fatigue and pain in RA therapy. Ann Rheum Dis 2018;77(SAT0182):952.

[182] Corominas H, et al. Correlation of fatigue with other disease related and psychosocial factors in patients with rheumatoid arthritis treated with tocilizumab: ACT-AXIS study. Medicine 2019;98:e15947. doi: 10.1097/md.0000000000015947.

[183] Rathbun AM, Harrold LR, Reed GW. A prospective evaluation of the effects of prevalent depressive symptoms on disease activity in rheumatoid arthritis patients treated with biologic response modifiers. Clin Ther 2016;38:1759–72 e1753. doi: 10.1016/j.clinthera.2016.06.007.

[184] Hansen IMJ, Emamifar A, Andreasen RA, Antonsen S. No further gain can be achieved by calculating Disease Activity Score in 28 joints with high-sensitivity assay of C-reactive protein because of high intraindividual variability of C-reactive protein: a cross-sectional study and theoretical consideration. Medicine 2017;96:e5781. doi: 10.1097/MD.0000000000005781.

[185] Masi AT, Aldag JC, Sipes J. Do elevated levels of serum C-reactive protein predict rheumatoid arthritis in men: correlations with pre-RA status and baseline positive rheumatoid factors. J Rheumatol 2001;28:2359–61.

[186] Shadick NA, et al. C-reactive protein in the prediction of rheumatoid arthritis in women. Arch Intern Med 2006;166:2490–4. doi: 10.1001/archinte.166.22.2490.

[187] Fleischmann RM, et al. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open 2017;3:e000382. doi: 10.1136/rmdopen-2016-000382.

[188] Hamann PDH, et al. Gender stratified adjustment of the DAS28-CRP improves inter-score agreement with the DAS28-ESR in rheumatoid arthritis. Rheumatology 2019;58:831–5. doi: 10.1093/rheumatology/key374.

[189] Kuriya B, et al. Thresholds for the 28-joint disease activity score (DAS28) using C-reactive protein are lower compared to DAS28 using erythrocyte sedimentation rate in early rheumatoid arthritis. Clin Exp Rheumatol 2017;35:799–803.

[190] Schoels M, Alasti F, Smolen JS, Aletaha D. Evaluation of newly proposed remission cut-points for disease activity score in 28 joints (DAS28) in rheumatoid arthritis patients upon IL-6 pathway inhibition. Arthritis Res Ther 2017;19:155. doi: 10.1186/s13075-017-1346-5.

[191] Pope JE, et al. Arthritis clinical trials at a crossroad. J Rheumatol 2015;42:14–7. doi: 10.3899/jrheum.140717.

[192] Agca R, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76:17–28. doi: 10.1136/annrheumdis-2016-209775.

[193] Crowson CS, et al. Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. Rheumatology 2017;56:1102–10. doi: 10.1093/rheumatology/kex038.

[194] Jagpal A, Navarro-Millán I. Cardiovascular co-morbidity in patients with rheumatoid arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment. BMC Rheumatol 2018;2:10. doi: 10.1186/s41927-018-0014-y.

[195] Yu Z, et al. Impact of changes in inflammation on estimated ten-year cardiovascular risk in rheumatoid arthritis. Arthritis Rheumatol 2018;70:1392–8. doi: 10.1002/art.40532.

[196] Alemao E, et al. Comparison of cardiovascular risk algorithms in patients with vs without rheumatoid arthritis and the role of C-reactive protein in predicting cardiovascular outcomes in rheumatoid arthritis. Rheumatology 2017;56:777–86. doi: 10.1093/rheumatology/kew440.

[197] Widdifield J, et al. Trends in excess mortality among patients with rheumatoid arthritis in Ontario, Canada. Arthritis Care Res 2015;67:1047–53. doi: 10.1002/acr.22553.

[198] Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009;11:229. doi: 10.1186/ar2669.

[199] Arvidson NG, Gudbjornsson B, Larsson A, Hallgren R. The timing of glucocorticoid administration in rheumatoid arthritis. Ann Rheum Dis 1997;56:27–31. doi: 10.1136/ard.56.1.27.

[200] Fleischmann R, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol 2017;69:277–90. doi: 10.1002/art.39944.

[201] Gabay C, et al. Identification of sarilumab pharmacodynamic and predictive markers in patients with inadequate response to TNF inhibition: a biomarker substudy of the phase 3 TARGET study. RMD Open 2018;4:e000607. doi: 10.1136/rmdopen-2017-000607.

[202] Huizinga TWJ, et al. Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis 2014;73:1626–34. doi: 10.1136/annrheumdis-2013-204405.

[203] Ismaili H, Ismaili L, Rexhepi M. Values and correlations between C-reactive protein and apolipoprotein B after treatment with methotrexate at patients with rheumatoid arthritis. Open Access Maced J Med Sci 2019;7:1293–8. doi: 10.3889/oamjms.2019.278.

[204] Kivitz A, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res 2014;66:1653–61. doi: 10.1002/acr.22384.

[205] Smolen JS, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet 2019;393:2303–11. doi: 10.1016/S0140-6736(19)30419-2.

[206] Burmester GR, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis 2017;76:840–7. doi: 10.1136/annrheumdis-2016-210310.

[207] Choy EH, Bernasconi C, Aassi M, Molina JF, Epis OM. Treatment of rheumatoid arthritis with anti-tumor necrosis factor or tocilizumab therapy as first biologic agent in a global comparative observational study. Arthritis Care Res 2017;69:1484–94. doi: 10.1002/acr.23303.

[208] Keystone EC, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400–11. doi: 10.1002/art.20217.

[209] van Vollenhoven RF, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19. doi: 10.1056/NEJMoa1112072.

[210] Genovese MC, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016;374:1243–52. doi: 10.1056/NEJMoa1507247.

[211] Kavanaugh A, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). Ann Rheum Dis 2017;76:1009–19. doi: 10.1136/annrheumdis-2016-210105.

[212] Abdallah H, et al. Pharmacokinetic and pharmacodynamic analysis of subcutaneous tocilizumab in patients with rheumatoid arthritis from 2 randomized, controlled trials: SUMMACTA and BREVACTA. J Clin Pharmacol 2017;57:459–68. doi: 10.1002/jcph.826.

[213] Wang J, Devenport J, Low JM, Yu D, Hitraya E. Relationship between baseline and early changes in C-reactive protein and interleukin-6 levels and clinical response to tocilizumab in rheumatoid arthritis. Arthritis Care Res 2016;68:882–5. doi: 10.1002/acr.22765.

[214] Burmester GR, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann Rheum Dis 2014;73:69–74. doi: 10.1136/annrheumdis-2013-203523.

[215] Fleischmann R, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol 2019;71:1788−800. doi: 10.1002/art.41032.

[216] van der Heijde, D. et al. SAT0058 consistency of radiographic responses with Sarilumab plus methotrexate across subpopulations of patients with rheumatoid arthritis in a phase 3 study. Ann Rheum Dis 2016;75:685. (SAT0058), doi: 10.1136/annrheumdis-2016-eular.

[217] Burmester GR, et al. SAT0202 Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with active rheumatoid arthritis in the phase 3 monarch study, including subpopulations. Ann Rheum Dis 2017;76 (SAT0202):849. doi: 10.1136/annrheumdis-2017-eular.4540.

[218] Boyapati A, et al. Sarilumab plus methotrexate suppresses circulating biomarkers of bone resorption and synovial damage in patients with rheumatoid arthritis and inadequate response to methotrexate: a biomarker study of MOBILITY. Arthritis Res Ther 2016;18 225. doi: 10.1186/s13075-016-1132-9.

[219] Juhl P, et al. IL-6 receptor inhibition modulates type III collagen and C-reactive protein degradation in rheumatoid arthritis patients with an inadequate response to anti-tumour necrosis factor therapy: analysis of connective tissue turnover in the tocilizumab RADIATE study. Clin Exp Rheumatol 2018;36:568−74.