A review on golimumab in the treatment of psoriatic arthritis.

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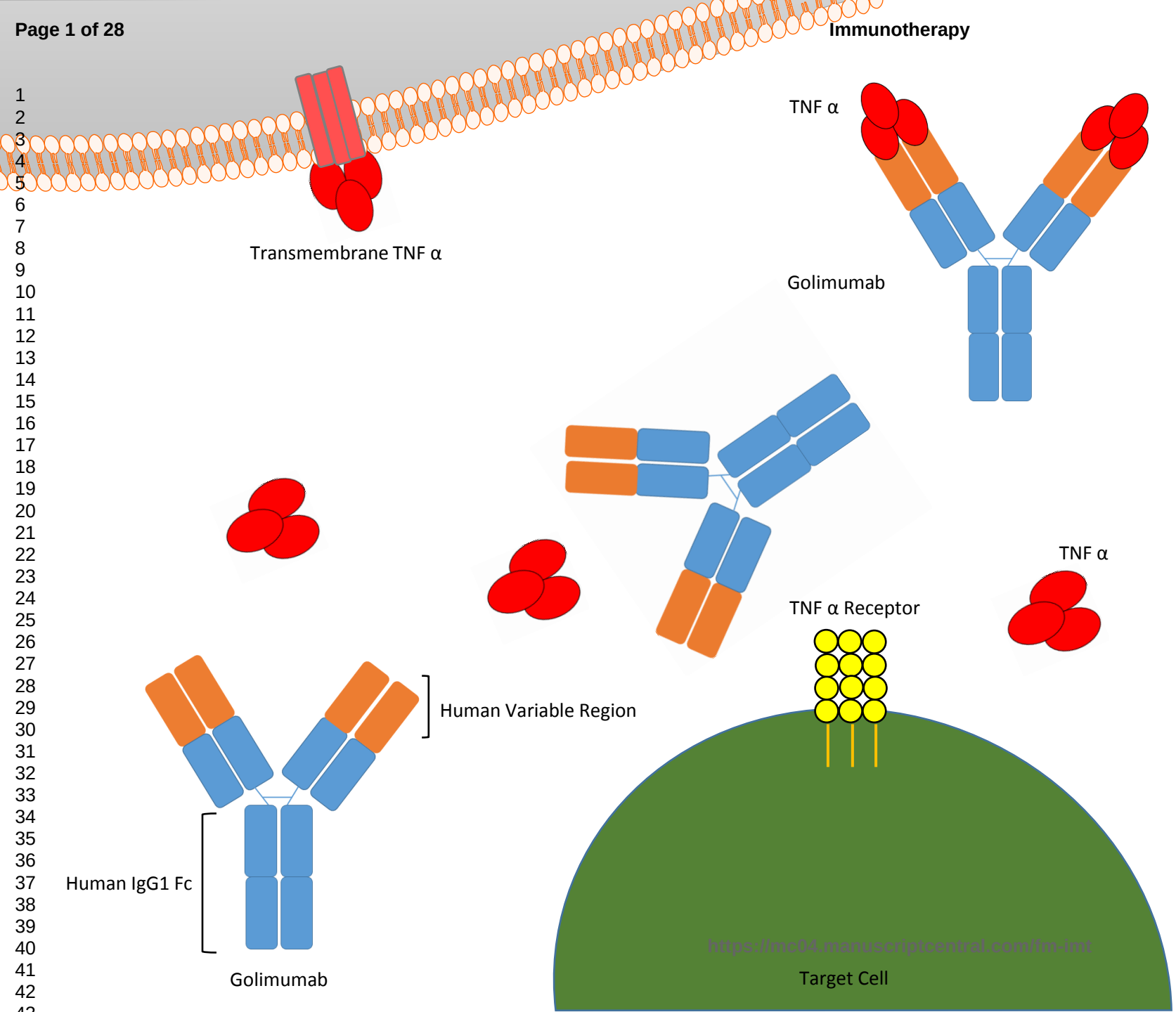

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A review on golimumab in the treatment of psoriatic arthritis

Abstract (120 words max)

Psoriatic arthritis causes inflammation in and around the joints and usually affects people who already have psoriasis. However, some patients develop the joint problems before the psoriasis. Currently there are five anti-TNF-α agents licensed for use in patients with psoriatic arthritis, Adalimumab, Certolizumab Pegol, Etanercept, Golimumab and Infliximab. Golimumab, a human monoclonal antibody, has been approved by the FDA for the treatment of psoriatic arthritis and is targeted against the pro-inflammatory molecule TNF-α. The phase III GO-REVEAL study confirmed this drug was well tolerated and showed significant improvement in disease activity compared to placebo.

Keywords Golimumab, psoriatic arthritis, monoclonal antibody, anti TNF-α, inflammation, Simponi.

Psoriatic arthritis (238)

Psoriatic arthritis (PsA) is a form of seronegative inflammatory arthritis that affects approximately 5% of patients with psoriasis [1]. In the majority of patients, skin lesions precede the onset of arthritis by several years. In 15% to 20% of patients the joint manifestations may precede the psoriasis. Occasionally both skin and joint manifestations appear simultaneously [1].

PsA typically presents with inflammatory joint pain and stiffness, and the disease can be divided into five subtypes based on the pattern of joints affected. PsA subtypes include: oligoarticular (<5 joints), polyarticular (≥5), distal interphalangeal (DIP)-predominant, spondylitis-predominant (+/- sacroiilitis) PsA and arthritis mutilans [2]. Although some of the features of PsA can mimic other forms of

inflammatory arthritis, unique features to PsA include DIP joint involvement, nail changes (most commonly pitting, onycholysis, transverse ridging and subungual hyperkeratosis), dactylitis and typical X-ray changes (lytic and periarticular new bone formation) [2]. Extra-articular features of PsA are less common than in other forms of inflammatory arthritis, however include synovitis of flexor tendon sheaths, conjunctivitis and acute anterior uveitis [1].

The diagnosis of PsA is based on the Classification Criteria for Psoriatic Arthritis (CASPAR), which consists of features of inflammatory joint disease with at least 3 points from the following [3]:

- Current psoriasis (2 points)
- Previous psoriasis (1 point)
- Family history of psoriasis, in the absence of the above (1 point)
- Dactylitis (1 point)
- Juxta-articular new bone formation on Xray (1 point)
- Rheumatoid factor (RF) negativity (1 point)
- Nail dystrophy (1 point)

Pathogenesis (581)

PsA is a complex multigenic disease which shows a high degree of familial aggregation, with up to 15% of a patient's relatives also being affected by PsA, and up to 30-40% having psoriasis [4]. Genes involved in the susceptibility of PsA include the Human Leukocyte Antigen (HLA) class I genes in the Major Histocompatibility Complex (MHC) and are fundamental to PsA pathogenesis. Alleles at the HLA-B and HLA-C loci are particularly noteworthy, with alleles *B*27*, *B*39* and *Cw*0602* playing key roles [4].

MHC molecules bind to and present soluble peptides to T cells, which in turn may trigger the T cell receptor; HLA class I to present peptides from cytoplasmic proteins to the T cell receptors of CD8+ lineage T cells [4]. The HLA alleles *B*27*, *B*39* and *Cw*0602* are believed to encode molecules that recognise self-peptides derived from proteins found in entheseal and synovial sites, and T cell clones specific for these self-peptides may be inappropriately activated via dendritic cells, and this activity is preserved by the continuous supply of self-peptides [4].

In addition to the MHC class I surveillance mechanism, natural killer (NK) cells, which originate from lymphocytes are key in the recognition of non-self and respond to molecules induced by inflammatory signals or cellular stress. Furthermore, NK receptors are found on CD8+ T cells [4]. An overbalance of stimulatory signals and triggering of the CD8+ T cells via NK receptor engagement may be accountable for triggering T cell clones and, via this mechanism, T cell clones with relatively low affinity for a target may be prompted to respond to self-peptides[4].

FitzGerald and Winchester hypothesised that a collection of T cells with T cell receptors that have low specificity for peptides expressed in the enthesis or the synovium, are differentiated to memory effector status and that NK cells from the innate immune system have their receptors engaged by these innate ligands. Ongoing inflammation and stress, which may be induced by infection or

trauma, may compensate for the diminished T cell receptor affinity for self-peptides and the clones may be triggered to expand and continue to mediate synovial tissue injury [4].

Synovial tissue in PsA is characterised by T and B cell infiltration, vascular proliferation and proliferating intimal synoviocytes [4]. Expression of pro-inflammatory cytokines (particularly, IL-1, 6, 12, 15, 17, 18, IFN-γ and tumour necrosis factor (TNF)-α have been recognised and cytokines such as TNFα, have also been demonstrated to be overexpressed in psoriatic plaques [4-5].

Curran et al investigated the character of the infiltrating T cells in PsA synovial fluid and tissues and demonstrated large expansions of CD8+ T cell clones, implicating the significant of the adaptive immune response in disease pathogenesis. As well as the presence of a background of non-clonally expanded polyclonal T cells which are thought to be triggered by circulating chemokines [5].

Furthermore, lymphoid aggregates expressing chemokines such as CXCL13 (and CCL21 are noted in associated with peripheral lymph node addressin-positive high endothelial venules [4]. Angiogenesis promoting factors are also upregulated, resulting in prominent vascular changes [4].

Ritchlin et al demonstrated that peripheral blood mononuclear cells from patients with PsA easily formed osteoclasts *in vitro* [7]. Receptor activator of NFκB (RANK)-positive perivascular mononuclear cells and osteoclasts have been demonstrated; additionally, RANK ligand expression was shown to be significantly upregulated in the synovial lining layer. It has been proposed that osteoclasts, derived from TNFα –activated peripheral blood mononuclear cells, migrate to the inflamed synovium and subchondral bone, at which point they are exposed to unopposed RANK ligand and TNFα resulting in osteoclastogenesis [7].

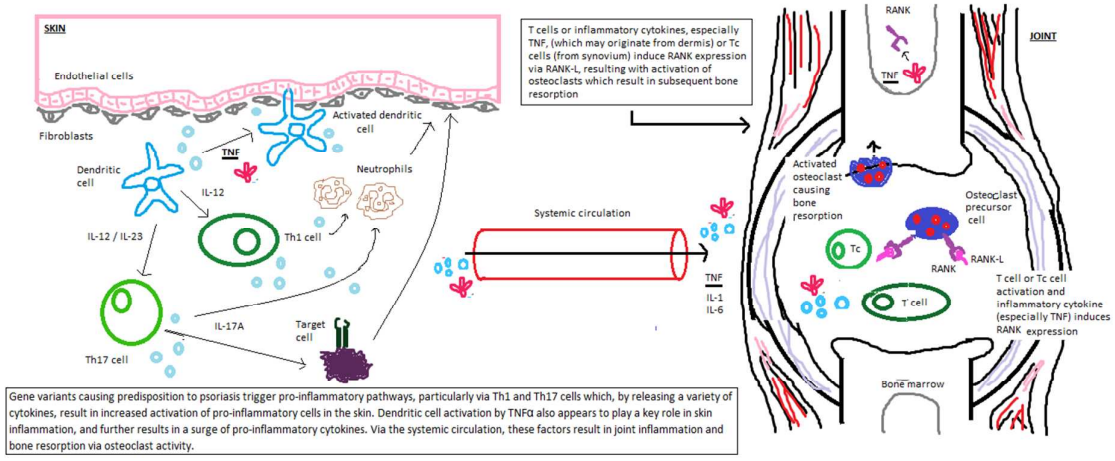

Figure 1. Cartoon depicting a proposed model of the pathogenesis of psoriatic arthritis.

Pharmacological treatments of PsA (584)

Current practice in the management of PsA is aimed at early diagnosis and intervention with disease-modifying anti-rheumatic drugs (DMARDs) and anti-tumour necrosis factor (TNF) therapies to

supress inflammatory processes and prevent long-term damage [8-9]. The management of PsA is targeted towards suppressing inflammation in the joints, tendons, entheses and skin. Patients with significant joint and skin/nail disease should ideally be managed by both Rheumatology and Dermatology specialists with therapies that can target all the clinical symptoms of PsA [9].

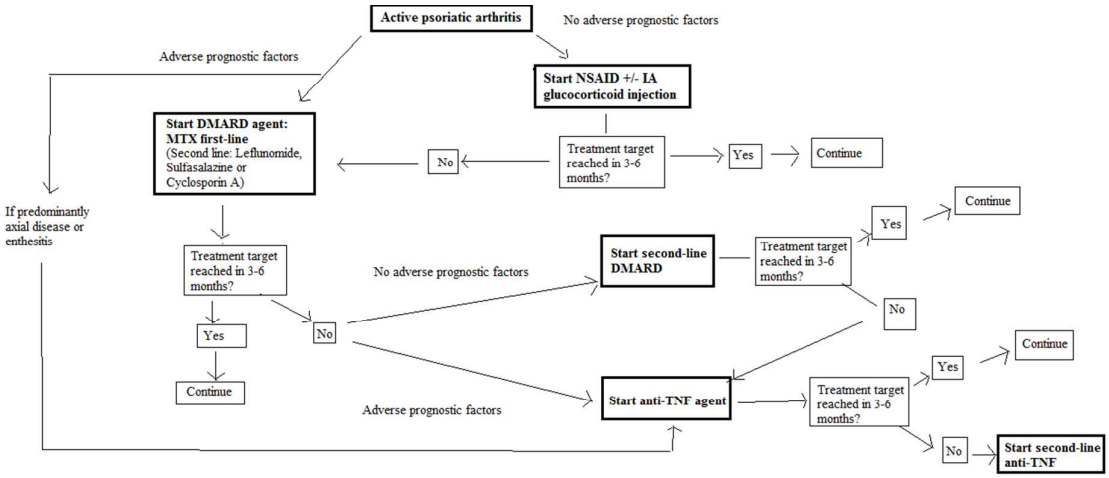

Figure 2. Treatment algorithm for PsA. Adapted from EULAR (European League Against Rheumatism) guidelines [9]. Abbreviations: DMARD (disease modifying anti-inflammatory drug), MTX (methotrexate), NSAID (non-steroidal anti-inflammatory drug), TNF (tumour necrosis factor).

The treatment algorithm for PsA according to the EULAR (European League Against Rheumatism) guidelines is dependent on whether a patient has adverse prognostic factors (APF), which include: either swollen or tender joint count >5, radiological joint destruction, elevated acute phase reactants and extra-articular manifestations such as enthesitis [9].

Patients with no evidence of APF should be initiated on (non-steroidal anti-inflammatory drug) NSAID therapy and their response assessed within 3-6 months; patients who fail to reach the treatment target (defined as remission or low disease activity) should be changed to DMARD (disease-modifying anti-rheumatic drug) therapy, of which the first line treatment is methotrexate. An intra-articular steroid injection can be given in limited disease, or if one joint if particularly symptomatic [9].

Patients with APF should be initiated on DMARD therapy and, if they have not reached the treatment target within 3-6 months, a second DMARD can be initiated if there are no APF. Those who do demonstrate APF at this point or show a lack of satisfactory response within 3-6 months should be changed to anti-TNF treatment [9].

Notably DMARD agents have been shown to have minimal effect on axial disease and/or enthesitis, and therefore these patients should be initiated directly onto anti-TNF therapy. In patients on anti-TNF therapy who fail to respond adequately within 3-6 months, a second-line anti-TNF drug could be started [9].

Anti-TNFα therapies in PsA

Currently there are five anti-TNFα agents which are licensed for use in patients in PsA [9-15]:

- Adalimumab (ADA): a fully human anti-TNFα monoclonal antibody.
- Certolizumab Pegol (CZP): a nanomolecule compromising a humanised Fab2 antibody fragment against TNFα with a polyethylene glycol tail.
- Etanercept (ETA): fusion protein consisting of the extracellular ligand-binding domain of the 75 kDa receptor for TNFα and the Fc portion of human IgG1.
- Golimumab: another fully human anti-TNFα monoclonal antibody.
- Infliximab (IFX): a chimeric anti-TNFα monoclonal antibody.

One of the first studies demonstrating the efficacy of anti-TNF therapy in modifying synovial cell populations and infiltrates in PsA was in 2001, where Baeten et al showed a reduction of vascularity and inflammatory cell populations following IFX treatment [10]. In this study, immunohistochemistry data demonstrated a marked reduction in vascular cell adhesion protein-1 expression on synovial endothelium and reduction of neutrophil and macrophage infiltration of the sub-lining layer; furthermore, a reduction of macrophage-like synoviocytes is noted. This is suggestive that anti-TNF agents result in endothelial deactivation, with reduction in both the vascularity and the migration and homing of inflammatory cells into the synovial tissue [11]. Furthermore, synovial lining thickness normalised within 12 weeks of treatment, which was associated with a significant reduction in the population of CD55-positive synovial lining fibroblasts [10].

In 2005, Kruithof et al showed reduced synovial lining layer thickness downregulation of both hypervascularity and of endothelial activation, leading to a reduction in inflammatory cell infiltrates in patients with spondyloarthropathy treated with IFX [13].

Introduction to the compound & Overview of market (417)

Golimumab (Simponi®) is a human monoclonal antibody, which is targeted against the pro-inflammatory molecule TNF-α [17]. It is licensed for the treatment of ulcerative colitis (UC), rheumatoid arthritis (RA), PsA and ankylosing spondylitis (AS); it can be used alone or in combination with methotrexate (MTX) [17].

Golimumab was characterized by Shealy et al in 2010 and is a recombinant human monoclonal antibody of IgG1 kappa subclass composed of two heavy chains (approximately 50 kDa each) and two lights chains (approximately 24 kDa each), with 16 disulphide bonds, and containing two N-glycans (Code Name: CNTO 148), see Figure 3 [18]. Golimumab is produced by a murine hybridoma

cell line with recombinant DNA technology. The drug product is manufactured by sterile filtration, aseptic filling and stoppering of pre-filled syringes, which are then assembled into a device for subcutaneous administration (single-use autoinjector or passive needle guard delivery system (UltraSafe) [19].

Golimumab is a human immunoglobulin G1k monoclonal antibody that binds with high affinity and specificity to both the soluble and transmembrane form of TNFα and neutralises their bioactivity by blocking interaction with TNFα a cell surface receptors (figure 3) [20]. The binding of human TNF-α by golimumab was shown to neutralise TNF-α-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule and intercellular adhesion molecule by human endothelial cells [21].

During golimumab characterisation it was compared with other anti-TNFs (IFX, ADA and ETA) to assess the affinity and in vitro TNF-α neutralization. The affinity of golimumab for soluble human TNF-α was significantly greater than ADA (p = 0.018), similar to ETA and greater than IFX. The concentration of golimumab required for TNF-α neutralisation by 50% was comparable to ETA and significantly less than IFX and ADA (P=0.017 and P=0.008, respectively) [18].

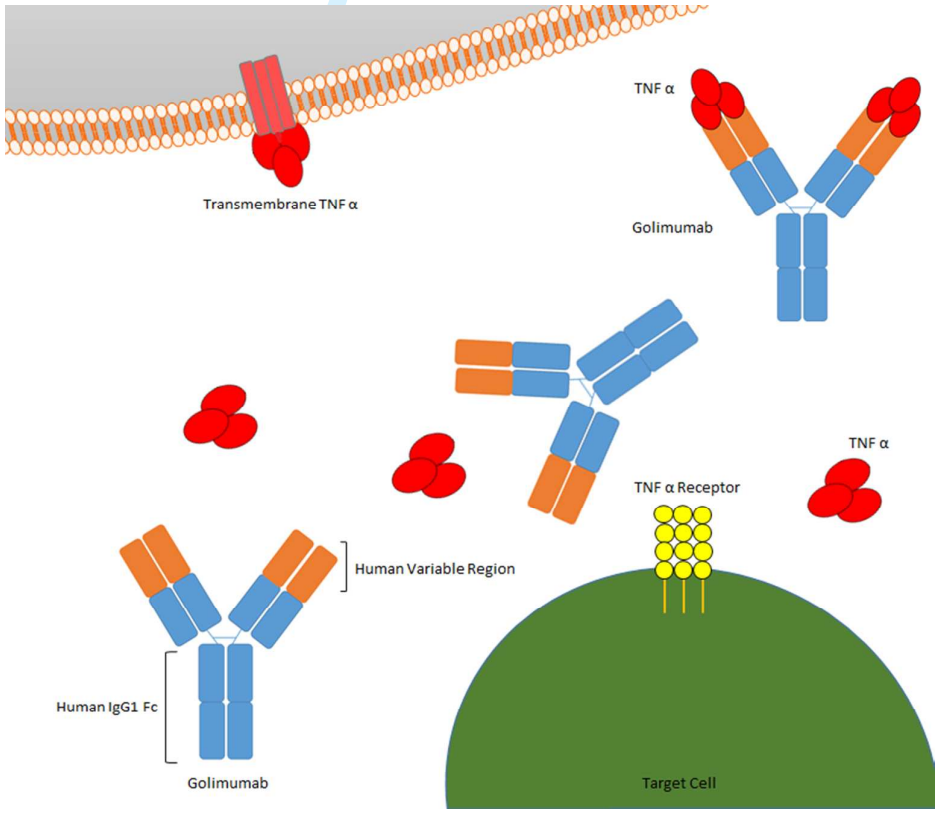

Figure 3. Mechanism of action of Golimumab binding to TNF α, preventing binding of TNF α to TNF α receptor on target cell. Golimumab monoclonal antibody structure with human variable regions and human IgG1 Fc [20-21].

In April 2009, Simponi™ was approved by the U.S. Food and Drug Administration (FDA) and Health Canada for the treatment of active PsA, moderately to severely active RA, and active AS. The European Medicines Agency (EMA) issued a positive opinion for granting a Marketing Authorisation to Golimumab in October 2009, as a once-monthly, subcutaneous therapy for the treatment of moderate-to-severe, active RA, active and progressive PsA and severe, active AS or non-radiographical axial spondyloarthritis [19]. In 2013 golimumab received approval for treatment of moderate to severe active UC. In addition, the EMA adopted a new indication for Golimumab in polyarticular Juvenile Idiopathic Arthritis (pJIA) in May 2016 [22]. Golimumab's current indication and posology approved by the EMA are summarized in table 1.

Table 1. Golimumab approved indication and posology [21].

Therapeutic indications		Posology*
Rheumatoid arthritis (RA)	Golimumab in combination with methotrexate (MTX), is indicated for: -treatment of moderate to severe, active RA in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate. -treatment of severe, active and progressive RA in adults not previously treated with MTX.	50 mg given once a month, on the same date each month. Golimumab should be given concomitantly with MTX.
Juvenile idiopathic arthritis: Polyarticular juvenile idiopathic arthritis (pJIA)	Golimumab in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with MTX.	50 mg administered once a month, on the same date each month, for children with a body weight of at least 40 kg.
Psoriatic arthritis (PsA)	Golimumab alone or in combination with MTX, is indicated for the treatment of active and progressive PsA in adult patients when the response to previous DMARD therapy has been inadequate.	50 mg given once a month, on the same date each month.
Axial spondyloarthritis	<u>Ankylosing spondylitis (AS):</u> Golmumab is indicated for the treatment of severe, active AS in adults who have responded inadequately to conventional therapy.	50 mg given once a month, on the same date each month.
	<u>Non-radiographic axial spondyloarthritis (nr-Axial SpA):</u> Golmumab is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).	50 mg given once a month, on the same date each month.
Ulcerative colitis (UC)	Golmumab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.	<u>body weight less than 80 kg:</u> initial dose of 200 mg, followed by 100 mg at week 2, then 50 mg every 4 weeks, thereafter. <u>body weight greater than or equal to 80 kg:</u> initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter

Patients with bodyweight greater than 100 kg For all of the above indications, in patients with RA, PsA, AS, or non radiographic Axial SpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse drug reactions with the 100 mg dose compared with the 50 mg dose. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Pharmacology (662)

Golimumab pharmacokinetics (PK) have been characterised in RA patients and in healthy volunteers. Golimumab exhibits dose-proportional PK in healthy volunteers over a dose range of 50mg to 400mg [21], and in patients with active RA over the dose range of 0.1 to 10 mg/kg following a single subcutaneous (SC) or intravenous (IV) dose, respectively [23]. After SC golimumab administration, peak concentrations are observed 3.5 days after the first dose (single dose), and 3.0 days after the 6th day of administration (multiple dose) [24]. Golimumab shows a slow absorption phase that masks the distribution phase, resulting in a monophasic decline serum concentration after SC injection, with a steady-state concentration being reached within 12 weeks [24]. However, after IV infusion serum golimumab concentration declined in a biphasic manner [24]. A summary of Golimumab pharmacokinetics parameters of single and multiple doses are summarised in Table 2.

Table 2. Summary of golimumab pharmacokinetic parameters single dose subcutaneous and intravenous (Mean ± SD) in rheumatoid arthritis patients and healthy volunteers [24-25].

RA PATIENT				
PARAMETERS	**SC**		**IV**	
	Single Dose	Multiple Dose	Single Dose	Multiple Dose
Dose	100 mg	100 mg/month	2 mg/kg	2 mg/kg/week12
Cmax (µg/mL)	5.1± 3.0	6.1 ± 3.7	44.4 ± 11.3	45.7 ± 16.1
Tmax* (d)	3.5 (2-7.1)	3 (1-15.1)	N/A	N/A
AUC0-t (µg.day/mL)	70.5 ± 41.0	89.1 ± 53.3	276.8 ± 65	303.4 ± 121.9
T1/2 (d)		13.1 ± 5.0		13.2 ± 2.9
CL (mL/d/kg)		19.7 ± 10.4		7.5 ± 2.6
Vss (mL/kg)		352.3 ± 216.0		98.8 ± 36.3

Healthy Volunteers		
PARAMETERS	**SC**	**IV**
	Single Dose	Single Dose
Dose	100 mg	100 mg
Cmax (µg/mL)	6.3 ± 2.8	29.5 ± 5.8
Tmax* (d)	4.0 (1.0-7.0)	N/A
AUC0-∞ (µg.day/mL)	100.1 ± 29.2	195.9 ± 48.9

T1/2* (d)	10.9 (6.5-21.3)	11.8 (6.6-18.0)
CL or CL/F (mL/d/kg)	13.8 ± 4.1	6.9 ± 2.0
Vz or Vz/F (mL/kg)	219.1 ± 65.1	115.1 ± 19.4
F (%)	51.1 ± 14.9	N/A

**Media (range)*

Following a single subcutaneous injection of 100mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51.1% ± 14.9% (Mean ± SD) [25]. Since golimumab exhibited approximately dose proportional PK following a subcutaneous administration, the absolute bioavailability of a golimumab 50mg or 200mg dose is expected to be similar [21]. The mean time to reach maximum serum concentration (6.3 µg/ml) in healthy subjects ranges from 1 to 7 days after the administration of 100mg SC [25]. During the assessment of golimumab PK in healthy volunteers it was observed that the volume of distribution of golimumab (115±19 ml/kg) was approximately twice the plasma volume, suggesting that golimumab is located primarily in the circulatory system with a small degree of extravascular tissue distribution [25].

A population PK analysis based on data obtained from patients with PsA in the GO-REVEAL pivotal study showed that body weight had a significant effect on both clearance and volume of distribution of monoclonal antibodies. The American College of Rheumatology improvement criteria observed a difference in the response rate of patients with a body weight greater than 100kg that were receiving 50mg of golimumab. Therefore, the effect of body weight on the PK parameters partially explains the trend of lower clinical response rates for Golimumab in patients weighing more than 100kg [20].

Afterwards, a population pharmacokinetic assessment of golimumab (SC) in patients with AS was performed by Xu et al 2010, concluding that body weight and anti-golimumab antibody status significantly influence golimumab clearance. The study revealed a tendency that patients with higher body weight had lower serum golimumab concentrations at steady state. Due to this significant relation of body weight on golimumab clearance, it has been indicated that patients weighing over 100kg and not showing adequate clinical response after 3 or 4 doses, should consider increasing the dose to 100mg once a month. The possible development of anti-golimumab antibodies should be considered in patients with golimumab therapy failure [26]. Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36% [21].

No ethnicity-related pharmacokinetic differences were observed between Asians and Caucasian subjects [27-28].

Anti-drug antibodies could influence golimumab pharmacokinetics, mainly increasing its clearance with a significant impact in golimumab efficacy. Patients who developed anti-drug antibodies generally had low trough steady-state serum concentrations of golimumab [21]. During population PK assessment, the antibody-to-golimumab status was identified as a significant covariate on CL/F [26]. Kneepkens et al, examined the relationship between anti-drug antibodies, golimumab levels

and clinical response in RA patients treated with golimumab, concluding that golimumab trough levels were higher in responders compared to non-responders after 1 year of treatment, with erythrocyte sedimentation Rate and C-reactive protein statistically significantly inversely associated with golimumab level over time [29]. Similar phenomena have been described during the assessment of golimumab in UC patients performed by Adedokun et al., observing an increase of golimumab clearance in relation to anti-drug antibodies [30].

Clinical efficacy (2022)

Golimumab's efficacy was evaluated in PsA patients in the GO-REVEAL Phase III study. This pivotal study was a randomised, double-blind placebo controlled study involving 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite NSAID or DMARD therapy, with stratification by baseline MTX use. Patients were naive to anti-TNF therapy with negative rheumatoid factor, had active plaque psoriasis (≥ 2cm diameter) and could not receive topical or systemic psoriasis treatments during the study [31-33].

The treatment groups were placebo SC (n=113), golimumab 50mg SC once every 4 weeks (n=146) and golimumab 100mg SC once every 4 weeks (n=146) [33]. The study participants were randomized 1:1.3:1.3 to one of the three treatment groups respectively. Patients may have taken stable doses of concomitant MTX (≤ 25 mg/week), oral corticosteroid (≤ 10mg prednisone/day or equivalent), and/or NSAIDs, but may not have taken systemic or topical psoriasis treatments/medications during the study [33].

During the GO-REVEAL study patients received the study treatment with placebo-control through week 24, followed by blinded golimumab treatment up to week 52, and open-label extension until week 256. At week 16, patients with no adequate response (<10% improvement from baseline in swollen and tender joints) could early escape from placebo to golimumab 50mg, or from golimumab 50mg to golimumab 100mg. At week 24, all patients that were still in the placebo group crossed over to golimumab 50mg group, such that all patients received golimumab 50 or 100mg every 4 weeks until week 252 [32-34].

The first co-primary efficacy endpoint assessed during the pivotal study was the proportion of patients with an American College of Rheumatology 20% improvement criteria (ACR20 response) at week 14. The ≥ 50% and 70% improvement criteria were assessed at endpoints ACR 50 and ACR70, respectively). ACR response assessment was based on the improvement in the swollen and tender joints count, and at least three of the following assessments: patient's assessment of pain, patient's assessment of disease activity, physician assessment of disease activity, health assessment questionnaire (HAQ), and C-reactive protein levels (CRP) [33,35].

The second co-primary efficacy endpoint was assessed from baseline in the total radiographic PsA-modified Sharp/van der Heijde score (SHS) of the hands and the feet at week 24 onwards and this endpoint was only to have been considered if the first co-primary endpoint was positive. [33,35].

Other supportive efficacy endpoints were Psoriatic Arthritis Response criteria, Disease Activity Score in 28 joints (DAS28), Psoriasis Area and Severity Index for 50%, 75% and 90% improvement (PASI50 PASI75 or PASI90), Nail Psoriasis Severity Index score, dactylitis and enthesis [31,33].

During the statistical assessment of the primary endpoint, superiority was assessed using a two-sided Cochran-Mantel-Haenszel test between combined golimumab groups vs the placebo group. If this was significant, a comparison of superiority was performed between Golimumab 100mg and placebo, and golimumab 50mg and placebo [33]. The pivotal study results were analysed and published through week 24 [31], week 52 [35], week 104 [34,36] and week 256 [32].

Golimumab vs. placebo resulted in statistically significant improvement in the primary endpoint of evaluation (ACR20 response) at week 14 (P <0.001), showing benefit with both 50mg and 100mg doses (51% and 45% of responders, respectively) and in the combined golimumab groups (48%) compared with placebo group response (9%). During week 24, the low and high dose golimumab groups demonstrated a greater proportion of statistically significant ACR20 responders than the placebo group (P <0.001). No differences were observed in the ACR response in patients receiving and not receiving concomitant MTX (P=0.66) [31]. These results supported the efficacy of golimumab with or without concomitant MTX in the treatment of PsA. Similar and consistent findings were observed during week 14 regarding ACR50 and ACR70 responses, and these treatment effects were maintained on increase at week 24. Both the golimumab treatment groups resulted in significantly greater improvement compared with placebo for each 7 ACR component in the study [31,33]. Table 3 displays the results of selected ACR endpoints of the pivotal study.

Table 3. Proportion of patients with American College of Rheumatology (ACR) responses in GO-REVEAL study [31,33].

	Placebo ± MTX	Golimumab 50 mg ± MTX	Golimumab 100 mg ± MTX	Combined Golimumab Groups ± MTX
N	113	146	146	292
ACR20				
Week 14	9%	51%	45%	48%
P value*		<0.001	<0.001	<0.001
Week 24	12%	52%	61%	57%
P value*		<0.001	<0.001	-
ACR50				
Week 14	2%	30%	28%	29%
Week 24	4%	32%	38%	35%
ACR70				
Week 14	1%	12%	17%	15%
Week 24	1%	19%	21%	20%

Radiographic images obtained at baseline, week 24 and week 52 were available for 400, 382, and 358 patients respectively [35]; and during week 104 and week 256 were available for 304 and 267 patients respectively [32]. Mean changes in radiographic PsA-modified SHS score of the hands and the feet from baseline to week 24 for the combined golimumab groups and for the golimumab 50mg group indicated significantly less radiographic progression in patients receiving golimumab than placebo (P=0.015 and P=0.011, respectively). No statistically significant differences were seen in the golimumab 100mg group vs placebo (P=0.086). The stratification of the results based on the baseline use of MTX showed that the golimumab-treated patients who were receiving concomitant baseline

MTX had less radiographic progression (P=0.003 Golimumab 50mg group+MTX vs Placebo and P=0.007 both golimumab groups+MTX vs Placebo) than patients who were receiving golimumab alone (P=0.495 Golimumab 50mg group+ MTX vs Placebo and P=0.350 both golimumab groups MTX vs Placebo) [35]. Radiographic benefit was maintained throughout the study until week 256 with golimumab, however at week 24 patients receiving MTX at baseline demonstrated less progression than patients not receiving MTX [32,36]. The overall 5 year radiographic progression showed the estimated annual radiographic progression was markedly reduced over the 256 weeks (calculated as baseline total score divided by baseline PsA duration) [32]. Table 4 displays the results of the week 24 second primary efficacy endpoint of the pivotal study.

Table 4. Summary of radiographic findings by randomized treatment groups in GO-REVEAL study, changes in PsA-modified SHS [32,34,35,36].

	Placebo ± MTX	Golimumab 50 mg ± MTX	Golimumab 100 mg ± MTX	Combined Golimumab Groups ± MTX
Week 24				
TOTAL SCORE				
N	113	146	146	292
Mean ± SD	0.27 ± 1.26	-0.16 ± 1.31	-0.02±1.32	-0.09±1.32
*P value**		***0.011***	***0.086***	***0.015***
MTX at Baseline				
N	55	71	71	142
Mean ± SD	0.22 ±1.25	-0.34 ±1.10	-0.16±1.36	-0.25±1.23
*P value**		***0.003***	***0.098***	***0.007***
NO MTX at Baseline				
N	58	75	75	150
Mean ± SD	0.31±1.28	0.01±1.47	0.11±1.28	0.06±1.38
*P value**		***0.495***	***0.340***	***0.350***
Week 52				
TOTAL SCORE				
N	113	146	146	292
Mean ± SD	0.22 ± 1.38	-0.22 ±1.64	-0.14 ±1.53	-0.18 ±1.59
MTX at Baseline				
N	55	71	71	142
Mean ± SD	0.06 ±1.23	-0.52 ±1.46	-0.38 ±1.82	-0.45 ±1.65
NO MTX at Baseline				
N	58	75	75	150
Mean ± SD	0.37 ±1.51	0.05 ±1.76	0.09 ±1.16	0.07 ±1.49
Week 104				
N	87	117	128	
Mean ± SD	0.08 ± 3.19	-0.39 ±2.04	-0.32 ±1.87	
MTX at Baseline				
N	51	61	63	
Mean ± SD	-0.24 ±2.09	-0.78 ±1.76	-0.65 ±2.15	
NO MTX at Baseline				
N	36	56	65	
Mean ± SD	0.53 ±4.30	0.03 ±2.25	0.00 ±1.51	

Week 256			
N	73	93	101
Mean ± SD	0.3 ±3.8	0.3 ± 4.2	0.1 ± 2.7
MTX at Baseline			
N	43	48	52
Mean ± SD	0.0 ±2.2	-0.3 ±4.8	-0.3 ±3.4
NO MTX at Baseline			
N	30	45	49
Mean ± SD	0.7 ±5.4	0.9 ±3.3	0.4 ±1.8
Mean ± SD			

During the assessment of secondary endpoints, golimumab appeared to be more effective than placebo at weeks 14 and 24 based on PsA response criteria, DAS28, CRP, PASI [31]. Golimumab treatment resulted in significant improvement in physical function as assessed by HAQ DI, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36 [21]. Significant improvements were observed in physical function, enthesis, dactylitis and skin manifestations, including 60% of patients achieving PASI75 improvement at week 256 [32]. No important changes in efficacy were seen between the different doses of golimumab (50mg vs 100mg). These findings were justified for the analysis limitation caused by the allowed dose changes [32].

In 2016, Kavanaugh et al, published a post-hoc analysis of long-term outcomes, assessing the achivement of Minimal Disease Activity (MDA) over 5 years period of time in GO-Reveal study. During this analysis MDA was defined as the presence of at least five of the following seven PSA outcome measures: swollen count ≤ 1 of 66 evaluated; tender joint count≤ 1 of 68 evaluated; PASI ≤ 1 (range 0-72); patient pain VAS score ≤ 15 (range 0-100); patient global assessment of disease activity VAS score ≤ 20 (range 0-100); HAQ DI score ≤ 0.5 (range 0-3); and tender enthesis points ≤ 1. This analysis included observed data from randomised patients with non-missing MDA and/or radiographic data at weeks 14, 24, 52, 104, 148, 196 and 256. In order to provide a reasonable number of patients available for analysis per treatment group, ≥ 3 and ≥ 4 consecutive timepoints were chosen as endpoints of MDA achievement, within the context of a clinically meaningful and sustained timeframe. Consequently 97% of randomised patients were included in this post-hoc analysis. The result showed statistically significant differences between golimumab group vs placebo with a higher proportion of patients achiving MDA in golimimab group when compared with placebo, during placebo-controlled period at week 14 and 24 ($P<0.0001$ and $P<0.0001$, respectively) (figure 4). Similar results were observed following the crossover to golimumab during week 52 ($P=0.037$), and baseline use of MTX did not influence the MDA achievement (figure 5). Achievement of MDA at ≥ 3 and 4 consecutive visits over the 5 years was associated with significantly less radiographic progression and higher improvement in MDA components (irrespective of treatment group) at week 256 vs patients not achievening MDA [34,37].

Interestingly patients who achieved persistent MDA and had MTX use at baseline demonstrated significantly less radiographic progression. After the post-hoc analysis Kavanaugh et al concluded that better long-term functional improvement, patient global assessment and radiographic outcomes were observed in golimumab-treated patients when patients achieved persistent MDA (excluding skin). Although 30% of all patients discontinued over the 5 year trial, the information obtained from the patients treated in Go-REVEAL was a good opportunity to perform the

restrospective evaluation of MDA, reflecting on the implications of achieving the treatment goal over a long period of time not explored to date. Based on these results, treatment with golimumab resulted in achievment of MDA in approximately 50% of patients through 5 years of treatment [34,37].

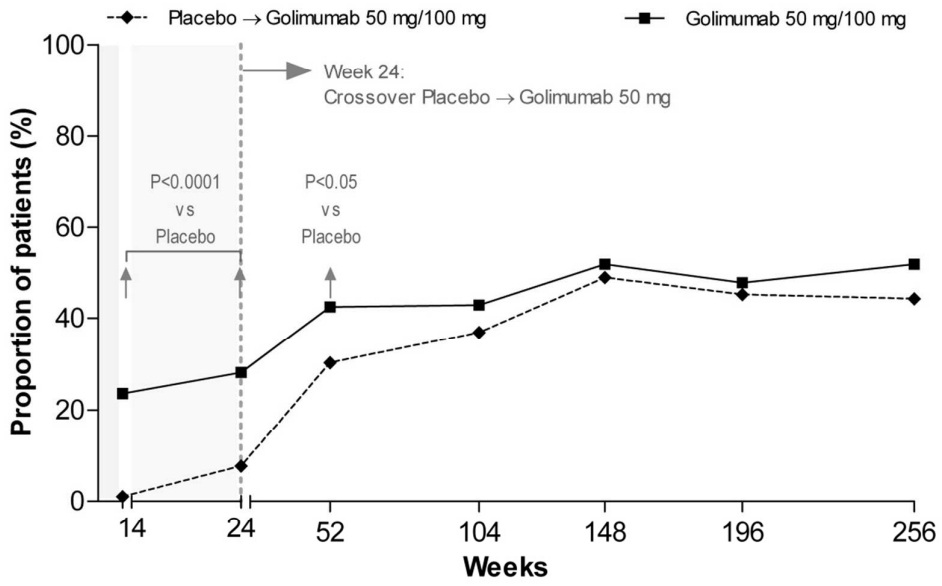

Figure 4. Achievement of Minimal Disease Activiy by randomised treatment and visits over 256 weeks (approximately 5 years). Figure created from data presented by Kavanaugh et al [37].

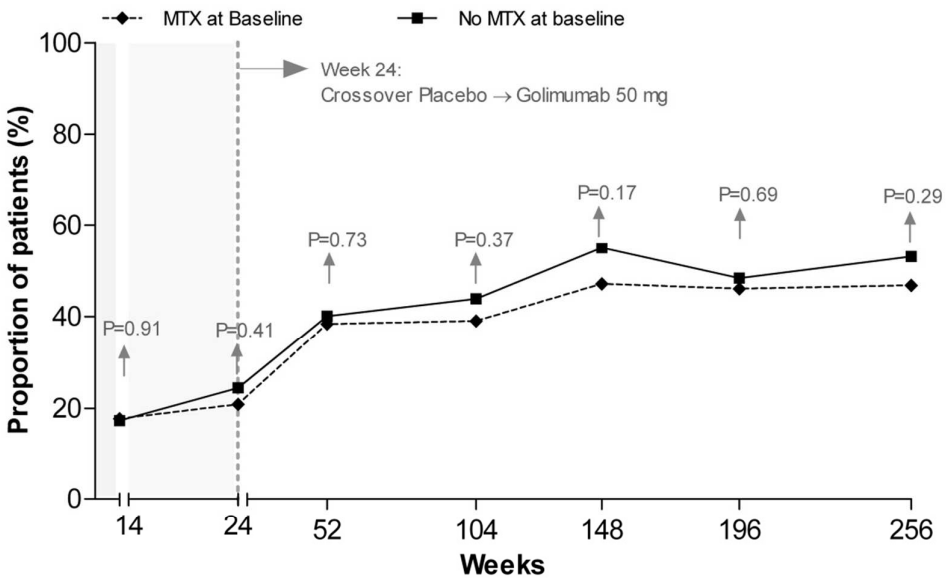

Figure 5. Achievement of Minimal Disease Activiy by randomised treatment and visits over 256 weeks (approximately 5 years) and by baseline methotrexate (MTX). Figure created from data presented by Kavanaugh et al table 1, including patients on active treatment (patients randomized to placebo who early escaped/crossed over at week 16/24 to receive golimumab 50 mg, with the possibility to increase golimumab from 50 to 100 mg after the week-52 database lock. And, Patients randomized to receive golimumab 50 mg who early escaped at week 16 or dose escalated after the week-52 database lock to receive golimumab 100 mg and also includes patients randomized to receive golimumab 100 mg [37].

No clinical trial with direct comparison of golimumab against other anti-TNFs have been found, however Fenix-caballero et al, performed an indirect comparison of the efficacy of ADA, ETA, IFX and golimumab in patient with PsA, based on phase III clinical trials with similar characteristics (population, duration and outcome). It concluded that these four anti-TNF inhibitors were more effective than placebo at 24 weeks based on the primary outcome (ACR50), but no statistical significant differences were observed between golimumab and the other treatments [38].

In 2016, a retrospective observational registry analysis of treatment patterns and health care resource utilisation (HCRU) in patients treated with SC anti-TNF inhibitor for immune-mediated rheumatic diseases was published. This analysis of treatment patterns and HCRU was performed in Switzerland between 2010 and 2012 in patients treated with SC anti-TNF inhibitor for immune-mediated rheumatic diseases. The study compared ADA, ETA, CZP and golimumab to assess the treatment persistence with anti-TNF inhibitor in patients with RA, PSA and AS [39].

The secondary endpoint assessed the potential effects on HCRU costs from non-treatment persistence. In total 4903 eligible participants were included in the study, and most patients were classified to specific rheumatic disease (52 % RA, 18% PsA and 21% AS). 70% and 79% of these patients were prescribed with NSAIDs and DMARDS, respectively. The investigators concluded that patients initiating treatment on golimumab were more likely to be persistent with their index therapy over the study period than patients on ADA or ETA (p=.022 and p=0.004, respectively), but no statistically significant differences were found between golimumab and CZP (p=0.075). The mean

total cost difference in non-biologic HCRU costs between persistent and non-persistent patients against baseline costs was statistically significant ($p<0.001$), including the cost for specialized outpatient care, in-patient care and non-DMARD medication [39].

In 2017 Iannone et al published a 2-year longitudinal study assessing the drug persistence of golimumab in unselected patients with RA, spondyloarthritis and PsA in standard of care settings, based on the assumption that patients in clinical practice may be quite different from randomised clinical trial patients, and that the time of persistence on therapy could be a surrogate marker of effectiveness and safety. Although differences between diseases were not assessed during this study, PsA patients included in the study fulfilled CASPAR criteria and were biologically-naïve or had inadequate response to prior biologic treatment, and were prescribed golimumab by their rheumatologist and used golimumab's posology approved by regulatory authorities. The main endpoints were persistence rate of golimumab in 2 years of treatment and the assessment of predictors of treatment discontinuation. The retention rate in the PsA cohort (181 patients) was 66.9 % at 2 years, mean survival time (MST) =19.0 (95% CI: 17.8-20.2 months). Gender was strongly associated with drug discontinuation with women having a twice the risk of discontinuation than men [40].

Medication adherence and treatment persistence over time was also assessed in a retrospective independent cohort study of patients with rheumatologic conditions newly initiating ETA, ADA, CZP, or golimumab. Whilst only 5% of the samples were on golimumab, results were suggestive of more adherence among patients initiating golimumab, but not with ADA or CZP compared to those initiating ETA. The authors concluded that rates of adherence and persistence to TNF inhibitor therapy were similar in the different rheumatologic conditions [41].

The persistence of golimumab treatment in rheumatology patients was assessed in a recent systematic review of data from clinical practice. Despite variability across the studies concerning persistence to golimumab, it was concluded that golimumab may have higher persistence compared to other agents, and suggested that persistence may be higher in biologic-naïve patients and in axial SpA (compared with RA and PsA). The authors stressed the need of further investigation on real-world persistence of golimumab, and comparing with other anti-TNF agents [42].

Safety and tolerability (1205)

Golimumab was demonstrated to be generally safe and well tolerated in first in human clinical trials. The phase III pivotal clinical trials including RA, PsA and AS patients; [4,6,7,9-15,43] showed the adverse events (AEs) profile across these populations seem to be comparable to other anti-TNFs [19,23,32,38,44-47]

During the first in human clinical trial the observed AEs were mild to moderate in intensity and had no clear dose-related trend in the incidence of AEs among golimumab dose cohorts (excluding headaches). The presence of anti-golimumab antibodies did not correlate with the incidence of AEs. No substantial differences were observed in the incidence of infections or infusion reactions between subjects who received placebo or golimumab [23].

Kavanaugh et al demostrated the long-term safety of the treatment in PsA patients over 5 years [32]. During the placebo-controlled phase the AEs at week 24 were 65% of all golimumab treated vs. 59% of placebo-treated patients. The serious adverse events (SAEs) were reported in 2% of all golimumab treated vs 6% of placebo-treated patients. The most common AEs observed in golimumab groups (mostly in the 100mg golimumab group) were nasopharyngitis and upper respiratory infections. Injection site reactions were observed in the same frequency in both groups. No differences were observed in hematology and biochemistry values between golimumab vs placebo groups, except for post-treatment alanine aminotransferase (ALT) and aspartate aminotransferase elevation in golimumab treated patients [31]. After week 24 no patients received placebo treatment as per study protocol, and the week 256 final assesmment showed no differences in the types of AEs observed between golimumab 50mg and golimumab 100mg groups. Injection-site reactions, occurred in 9% of patients during week 268, but the incidence of anti-drug antibodies did not appear to be related with this local reaction. No patient experienced anaphylactic or serum sickness-like reactions. Week 256 common laboratory abnormalities were elevated eosinophil count and total bilirubin. There were no relevant differences in safety outcomes between the 50mg and 100mg golimumab groups, except for opportunistic infections only reported in the 100mg group. Malignancies were observed in 21 patients through week 268, including 10 patients with non-melanoma skin cancer and 11 patients with other non-lymphoma malignancies (breast, bladder, colon, oesophageal, prostate and smal-cell lung cancer); but the authors concluded that all malignancies observed in the study were not different from those expected in the general US population, except for non-melanoma skin cancer [32].

The five-year safety analysis of golimumab provided safety information from 5 pivotal clinical trials with 2228 patients with RA (GO-BEFORE, GO-FORWARD and GO-AFTER studies), PsA (GO-REVEAL study) and AS (GO-RAISE study). This analysis included placebo-controlled and uncontrolled study periods. AEs were reported in 73.6% of patients in the placebo group against 92.8% of 50mg golimumab and 95.5% 100mg golimumab. The common AEs were; infections, constitutional symtoms, hypertension, injection site erythema and elevated ALT levels. Increased incidence of active tuberculosis (TB) and opportunistic infections (toxoplasmal eye infection, histoplasmosis and P. legionella) were observed in golimumab 100mg group vs golimumab 50mg group. The fact that placebo-controlled period was relatively short seems to be a limitation of this analysis, however the authors concluded that the observation of 2228 patient treated with golimumab over 5 years provide a relevant evidence of the safety profile (summary in table 5) [47].

Table 5. Safety findings through 5 years: pooled data from phase III studies of golimumab SC in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis patients [47]. Number of patients with AEs and percentage of patients with AEs are highlighted.

	Placebo	Golimumab 50 mg	Golimumab 50 mg & Golimumab 100 mg	Golimumab 100 mg	All Golimumab
Number of patients	639	671	765	792	2228
Most Common AEs*					
Patients with ≥ 1 AE	470 (73.6%)	623 (92.8%)	704 (92.0%)	756 (95.5%)	2083 (93.5%)
Upper respiratory tract infection	56 (8.8%)	215 (32.0%)	227 (29.7%)	246 (31.1%)	688 (30.9%)
Nasopharyngitis	41 (6.4%)	117 (17.4%)	152 (19.9%)	164 (20.7%)	433 (19.4%)

Bronchitis	24 (3.8%)	92 (13.7%)	114 (14.9%)	114 (14.4%)	320 (14.4%)
Back pain	22 (3.4%)	91 (13.6%)	116 (15.2%)	112 (14.1%)	319 (14.3%)
Cough	38 (5.9%)	93 (13.9%)	97 (12.7%)	112 (14.1%)	302 (13.6%)
Headache	39 (6.1%)	91 (13.6%)	88 (11.5%)	114 (14.4%)	293 (13.2%)
Sinusitis	15 (2.3%)	86 (12.8%)	108 (14.1%)	95 (12.0%)	289 (13.0%)
Arthralgia	29 (4.5%)	87 (13.0%)	98 (12.8%)	99 (12.5%)	284 (12.7%)
Nausea	51 (8.0%)	63 (9.4%)	94 (12.3%)	127 (16.0%)	284 (12.7%)
Hypertension	17 (2.7%)	66 (9.8%)	112 (14.6%)	101 (12.8%)	279 (12.5%)
Diarrhea	36 (5.6%)	69 (10.3%)	80 (10.5%)	96 (12.1%)	245 (11.0%)
Urinary tract infection	20 (3.1%)	53 (7.9%)	75 (9.8%)	87 (11.0%)	215 (9.6%)
RA	26 (4.1%)	34 (5.1%)	88 (11.5%)	75 (9.5%)	197 (8.8%)
Fatigue	26 (4.1%)	48 (7.2%)	51 (6.7%)	84 (10.6%)	183 (8.2%)
Injection site erythema	7 (1.1%)	39 (5.8%)	50 (6.5%)	86 (10.9%)	175 (7.9%)
ALT increased	33 (5.2%)	80 (11.9%)	65 (8.5%)	83 (10.5%)	228 (10.2%)
ALT increased	33 (5.2%)	80 (11.9%)	65 (8.5%)	83 (10.5%)	228 (10.2%)
Most Common SAEs*					
Patients with ≥ 1 SAE	58 (9.1%)	177 (26.4%)	230 (30.1%)	275 (34.7%)	682 (30.6
Pneumonia	5 (0.8%)	11 (1.6%)	22 (2.9%)	13 (1.6%)	46 (2.1%)
RA	6 (0.9%)	6 (0.9%)	14 (1.8%)	14 (1.8%)	34 (1.5%)
Osteoarthritis	0	6 (0.9%)	16 (2.1%)	8 (1.0%)	30 (1.3%)
Basal cell carcinoma	3 (0.5%)	5 (0.7%)	8 (1.0%)	13 (1.6%)	26 (1.2%)
Cholelithiasis	1 (0.2%)	4 (0.6%)	5 (0.7%)	11 (1.4%)	20 (0.9%)
Sepsis	0	1 (0.1%)	7 (0.9%)	11 (1.4%)	19 (0.9%)
Arthralgia	0	2 (0.3%)	6 (0.8%)	8 (1.0%)	16 (0.7%)
** Values are n (%)*					

During the indirect comparison of ADA, ETA, IFX and golimumab in patients with PsA performed by Fenix-caballero et al, it was concluded that upper-airway infection was the most frequent adverse reaction in all the drugs assessed. Significant differences were observed in relation to reaction at the site of injection between golimumab vs ETA, with greater proportion of reactions in patients receiving ETA [38].

Iannone et al concluded that golimumab was safe and well tolerated during the 2 year-long longitudinal study assessing golimumab in patients with RA, SpA and PsA in standard of care settings. This study was based on the assumption that time of persistence on therapy could be a surrogate marker of effectiveness and safety. During the assessment of the result it was observed that 4.8% of patients stopped treatment due to AEs, and 19.2% due to lack of efficacy. The AEs related to treatment interruption were gastrointestinal AEs, shingles, pulmonary AEs, neoplasia (breast cancer, ovarian cancer and meningioma), haematological AEs (neutropenia and thrombocytopenia), peripheral neuropathy, cerebral vasculopathy, dental abscess, skin rash and flare of skin psoriasis [40].

In general anti-TNF drugs have been well tolerated, but some AEs have raised concerns regarding development or reactivation of serious infections and the increased risk of cancer. A recent systematic review and meta-analysis performed by Minozzi et al. assessed the risk of infections using anti-TNF agents (ADA, CZP, ETA, golimumab, or IFX) in RA, PsA, and AS, including data from 71 randomised controlled trials (22,760 participants) and 7 open-label extension studies (2,236 participants) that reported the occurrence of infectious AEs (serious infections; TB; opportunistic infections; any infection). Statistically significant increases in the occurrence of any infections (20%), serious infections (40%), and TB (250%) were found associated with anti-TNF drug use; and did not identify substantial differences among the anti-TNF drugs. The use of anti-TNF drugs were associated

with increased risk of serious infectious AEs, under both a fixed-effects and a random-effects model. The subgroup analysis to assess the risk by anti-TNF drugs (ADA, golimumab, IFX, CZP, or ETA) suggested that ETA and golimumab might have a better safety profile for serious infections. Despite the limitation of the analysis, the authors found the findings in line with several observational studies reporting a significant rise in the risk of infectious AEs associated with anti-TNF drug use [48].

In regard to malignancy risk, Bonovas et al, performed a systematic review and meta-analysis to assess the effect of anti-TNF agents on the occurrence of any type of cancer in adult patients with rheumatologic disease, observing a total of 112 malignancies in 32 randomised controlled trials involving 15,539 patients, and concluded that the analysis did not provide evidence to conclude that the use of anti-TNF drugs significantly affects cancer risk in adult patients with rheumatologic disease. Exposure to anti-TNF agents was not associated with cancer risk, under both a fixed-effects (OR: 1.30, 95% CI: 0.86, 1.98) and a random-effects model (OR: 1.16, 95%CI: 0.73, 1.85), and in the specific case of patient with PsA the exposure to anti-TNF agents was also not associated with cancer (three trials; 1014 participants; fixed-effects OR: 1.57, 95% CI: 0.29, 8.49; and random- effects OR: 1.34, 95% CI: 0.17, 10.5). Furthermore the authors explained that the analysis of sub-groups according to the type of anti-TNF agent did not demonstrate any statistically significant association between ADA, golimumab, IFX, CZP, or ETA and cancer risk. They concluded that the observed evidence supported the hypothesis that the use of anti-TNF agents does not significantly affect cancer risk in the short term, but also suggested that it is important to continue monitoring their long-term safety profiles (e.g. post-marketing surveillance, registries and long-term epidemiological studies) [49].

In general, as with other anti-TNFs, golimumab should be used with caution or not used in patients with serious infections (including TB), invasive fungal infections, Hepatitis B reactivation, malignancies and lymphoproliferative disorders, congestive heart failure, demyelinating disorders, lupus-like syndrome and hypersensitivity reactions. Additionally patients with latex allergy should not handle the needle cover on the prefilled syringe, because it contains dry natural rubber (a derivative of latex) [21,50].

Regulatory affairs (62)

Janssen Biotech, Inc. discovered and developed SIMPONI® and markets the product in the United States. Since FDA approval in 2009, golimumab has been licensed for use in the treatment of rheumatic diseases in different countries around the world (table 6). In 2011, after an arbitration proceeding, golimumab distribution rights in Europe, Russia and Turkey were licensed to Merck Sharp & Dohme Limited [51,52,53].

Table 6. Summary of marketing rights in countries in which golimumab is licensed for use [51,52,53].

Company	Countries
Janssen Biotech Inc. (formerly Centocor Biotech Inc.)	USA

Janssen Pharmaceutical Companies (Johnson & Johnson)	Canada, Central and South America, the Middle East, Africa and Asia Pacific
Mitsubishi Tanabe Pharma Corporation	Japan, Indonesia, Taiwan
Merck Sharp & Dohme Limited	Europe, Russia and Turkey

Summary (160)

The pathogenesis of PsA is complex, and numerous inflammatory cells and cytokines have been implicated, of which TNF-α appears to play a key role [4,6].

At present, there are five anti-TNF-α agents licensed for use in patients with PsA, consisting of a fusion protein consisting of a ligand-binding for a TNF-α receptor and the Fc portion of human IgG1 (Etanercept), a nanomolecule containing a fragment against TNF-α (Certolizumab Pegol) and three monoclonal antibodies (Infliximab, Adalimumab and Golimumab) [16]. Of the monoclonal antibodies, Infliximab is a chimeric anti-TNF-α antibody, whereas the latter two are fully humanised [16].

In 2009, golimumab was approved by the FDA and the subsequent phase III GO-REVEAL study demonstrated this drug was well tolerated and showed improvement in disease activity according to ACR criteria 20/50/70 compared to placebo. Additionally, golimumab demonstrated improvements in PsA response criteria, DAS28 CRP and PASI. [31,32,34,35,36,37].

Executive Summary

Etiology:

- PsA is a form of seronegative inflammatory arthritis affecting up to 42% of patients with psoriasis
- PsA is divided into 5 subtypes: oligoarticular (<5 joints), polyarticular, distal interphalangeal (DIP)-predominant, spondylitis-predominant (+/- sacroiilitis) PsA and arthritis mutilans
- It is a complex, multigenic disease involving a plethora of inflammatory cells and cytokines, of which TNF-α is key

Treatment:

- The treatment of PsA depends on whether poor prognostic factors of disease are present (swollen or tender joint count >5, radiological joint destruction, elevated acute phase reactants and extra-articular manifestations, in particular enthesitis)
- Patients with poor prognostic factors should be initiated on DMARD therapy; if remission or low disease activity is not achieved, anti-TNF agents are indicated

- Patients with predominantly axial disease or enthesitis should be started on anti-TNF therapy as first-line
- Five anti-TNF agents are currently licensed for use in PsA, including Adalimumab, Certolizumab Pegol , Etanercept, Golimumab and Infliximab,

Golimumab:

- Golimumab is a human monoclonal antibody which is targeted against the pro-inflammatory molecule TNF-α
- Results from the phase III GO-REVEAL study show a significant improvement in PsA disease activity in patients treated with Golimumab compared to placebo

Conclusion:

- Golimumab provides an alternative anti-TNF agent for use in the treatment of PsA and demonstrates good efficacy and safety profile in a large, phase III clinical trial

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