HUMAN VACCINES & IMMUNOTHERAPEUTICS
2021, VOL. 17, NO. 6, 1586–1598
https://doi.org/10.1080/21645515.2020.1836919

Taylor & Francis
Taylor & Francis Group

PRODUCT REVIEW

Golimumab (anti-TNF monoclonal antibody): where we stand today

Ana Teresa Melo[a,b], Raquel Campanilho-Marques[a,b], and João Eurico Fonseca[a,b]

[a]Rheumatology Department, Hospital De Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal; [b]Rheumatology Research Unit, Instituto De Medicina Molecular João Lobo Antunes, Faculdade De Medicina, Universidade De Lisboa, Lisbon, Portugal

ABSTRACT

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine and its overexpression has been implicated in the pathophysiology of several chronic immune-mediated inflammatory diseases. Biological therapies, like TNF inhibitors, have been revolutionizing the course of these disorders. Golimumab is a transgenic anti-TNF monoclonal antibody that acts primarily by targeting and neutralizing TNF, thus preventing inflammation. It is approved for the treatment of Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Nonradiographic axial Spondyloarthritis, Juvenile Idiopathic Arthritis, and Ulcerative Colitis. Clinical trials are also being conducted in other conditions. This review charts the clinical development of golimumab and outlines the data that support its potential use across several Immune-mediated inflammatory diseases.

ARTICLE HISTORY
Received 31 July 2020
Revised 17 September 2020
Accepted 9 October 2020

KEYWORDS
Immune-mediated inflammatory diseases; tnf inhibitors; golimumab

Introduction

Chronic immune-mediated inflammatory diseases are responsible for loss of quality of life, disability, and incur substantial costs to patients and society.[1] Thus, there has been a great investment in the development of effective therapies for these diseases.

The inflammatory cytokine tumor necrosis factor (TNF) is a pleiotropic cytokine that is produced by activated macrophages, T lymphocytes, monocytes, neutrophils, mast cells, endothelial cells, fibroblasts, and osteoclasts. It has been identified as a master pro-inflammatory cytokine and overexpression of TNF has been implicated in several chronic immune-mediated inflammatory disorders. It stimulates the production of other pro-inflammatory cytokines such as interleukin (IL) 1 and IL-6, chemokines, adhesion molecules, nitric oxide, and prostaglandins. In addition, it activates neutrophils and eosinophils, increases endothelial layer permeability, and interferes with the intestinal barrier function.[2] TNF promotes angiogenesis, influences tissue remodeling and activates osteoclasts, leading to focal joint erosions and skeletal osteoporosis. It has broad effects on the modulation of the immune system and induction of immune cell apoptosis and directly mediates pain, fever and cachexia.[3]

There are two forms of TNF: a soluble cytokine, sTNF (17 kDa), and a transmembrane TNF (tmTNF), a 26 kDa protein. The first results from the cleavage of tmTNF by a metalloproteinase, TNF-converting enzyme. Both forms can bind to TNF receptor 1 (TNFR1) or TNFR2.[4]

According to the metabolic state of the cell, sTNF and tmTNF receptor-mediated effects can lead to activation of nuclear factor-κB (NF-kB) or to apoptosis. Although TNFR1 signaling pathways are better characterized, TNFR2 appears to have both shared and opposing effects to TNFR1 and may be actively involved in the pathogenesis of inflammatory diseases. It also seems to be the preferential receptor for tmTNF.[5]

Different TNF inhibitors (TNFi) act in one or both forms of TNF and exert several effects besides TNF neutralization.[6,7] In fact, several studies in mice and humans suggest that TNF blockade has the potential to augment regulatory T cell (Treg) numbers and function. For instance, Nguyen et al[8] demonstrated that adalimumab promoted the interaction between tmTNF on monocytes and TNFR2 on Tregs in Rheumatoid Arthritis (RA) patients, resulting in the expansion of functional Foxp3-positive Tregs. In addition, TNFi modulate the expression of adhesion proteins, such as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Finally, TNFi promote apoptosis by blocking TNFR signaling and thereby NF-kB activation and transcription of survival signals. Most recent data suggest that TNFi induce apoptosis in immune cells via activation of reverse signaling pathways. Cell cycle G0/G1 arrest and apoptosis occurs in tmTNF-expressing Jurkat T lymphocytes that neither express TNFR1 nor TNFR2. c-Jun N-terminal protein kinase (JNK) activation followed by up-regulation of p21WAF1/CIP1, Bax, Bak and reactive oxygen species accumulation are important intracellular signaling actions for those events. TNFi that are full-length monoclonal antibodies (mAb) also possess constant region (Fc)-effector activity. They induce antibody-dependent cellular cytotoxicity (ADCC) and activate the complement pathway leading to cell-dependent cytotoxicity (CDC) and apoptosis.[5] All these complex mechanisms contributing to the resolution of inflammation are still being investigated.[9]

CONTACT Ana Teresa Melo anateresamelo@campus.ul.pt Rheumatology Department, Hospital De Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon Academic Medical Centre, Instituto De Medicina Molecular João Lobo Antunes, Faculdade De Medicina, Universidade De Lisboa, Lisbon, Portugal

Higher TNF levels have been detected in serum and in inflamed tissues of patients with immune-mediated inflammatory diseases.[10,11] This suggests that there is local production of this cytokine.[12] The involvement of TNF in the pathomechanisms of these diseases is further suggested by studies showing that the serum and lesional amounts of this cytokine decrease after effective therapy.[13,14]

In RA patients higher TNF levels have been identified in synovial fluid and at the interface of the distinct cartilage-pannus junction, target of joint damage. TNF stimulates fibroblast growth and induces collagenase and prostaglandin release from adherent synovial cells and fibroblasts.[12]

In inflammatory bowel disease (IBD) TNF concentration is abnormally high in the gut mucosa. Biopsies from uninflamed areas also had substantial numbers of T cells, monocytes, and macrophages, which could induce the production of TNF.[13]

Elevated TNF levels have been measured in the epidermis of psoriatic plaques. Stimulated keratinocytes may act as initiators of an inflammatory process. After stimulation, keratinocytes release pro-inflammatory mediators, like TNF, which are able to induce the expression of adhesion molecules on endothelial cells and the recruitment of circulating immunocytes. The interaction between keratinocytes and activated T lymphocytes leads to an increased proliferation of keratinocytes that are genetically predisposed.[14]

There are five TNFi commercially available: infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab.

All five TNFi bind to tmTNF on tmTNF-transfected cells with similar affinities that are lower compared to sTNF.[5] Effector functions of tmTNF as a ligand are inhibited by any of the TNFi agents, although the activity of etanercept is weaker than the other agents; differences may come from stoichiometric variances.

Infliximab is a chimeric mouse/human anti-TNF mAb composed of a murine immunoglobulin (Ig) heavy (H) and κ light (L) chain variable regions (Fab) with specificity for human TNF, and a human IgG1 Fc.[5] It was obtained by genetic engineering techniques and the murine constant regions was replaced with human counterparts while retaining the murine antigen-binding regions.[15] Adalimumab is a human IgG1 mAb developed using phage-display technology based on Chinese hamster ovary cells.[16] Etanercept is a fusion protein, comprising the Fc portion of human IgG1 and the extracellular domain of the human TNFR2 receptor It is synthesized in Chinese hamster ovary cells by recombinant DNA technology.[17] Certolizumab is a monovalent Fab fragment of a humanized anti-TNF antibody conjugated with two cross-linked chains of polyethylene glycol (PEG) lacking the Fc region. The construct is expressed in *Escherichia coli* bacteria.[18] Golimumab was derived from transgenic mice, produced by knocking human immunoglobulin genes into the murine genome, engineered to express human IgGs.[7] Accordingly, golimumab was expected to be associated with less immunogenicity. Thomas et al.[19] documented in a systematic review that after etanercept [(1.2% of the patients producing anti-drug antibodies (ADAs)], golimumab was the least immunogenic (3.8%) of the TNFi, whereas the most immunogenic was infliximab (25.3%), followed by adalimumab (14.1%) and certolizumab (6.9%). Shealy et al.[2] reported that the affinity of golimumab to sTNF is superior to those of infliximab and adalimumab and that conformationally, golimumab is more stable. The inhibitory ability of golimumab against TNF-induced cytotoxicity and activation of human endothelial cells also seems to be greater.

Over the following sections we will characterize the pharmacokinetics, immunogenicity, clinical efficacy, and safety of golimumab.

Golimumab – overview

Rodent monoclonal antibodies are easily obtained, however, their immunogenicity limits their use. Different approaches have been used to overcome this, like the generation of transgenic mice comprising human heavy and light chain Ig loci.[20] In this technique, mice are modified to express human IgG and immunized with recombinant human TNF.[16] Golimumab was originally isolated from a hybridoma clone transgenic mice that had been immunized with human TNF. The golimumab-secreting clone was selected after being assayed for TNF-binding.[2,16]

The heavy and light variable chain regions of golimumab are formed of an amino acid sequence virtually identical to those of the human sequence (heavy chain sequence, 98%; light chain sequence, 100%). The Fab region is specific for human TNF and is bivalent, which allows binding to both sTNF and tmTNF. Thus, it decreases the circulation of TNF and the binding of TNF to receptors. The amino acid sequence of the Fc regions are identical to those of infliximab. The relative affinity of the Fc portion of golimumab to Fc receptors is unknown but is likely to be related to biologic effects. It is expected to have actions comparable to those of other TNFi with Fc components (infliximab, adalimumab, and etanercept) concerning ADCC, CDC, reverse signaling, and cytokine suppression.[21,22]

The preclinical safety and immune-modulating effects of golimumab were evaluated in 16 cynomolgus macaques. The animals were treated with either saline, 10 mg/kg golimumab or 50 mg/kg golimumab doses administered twice per week by subcutaneous (SC) injection for up to six months. Immune system function was assessed by production of IgG and IgM. There were no signs of toxicity or histopathological changes in lymphoid tissues and no animal developed an infection. The investigators concluded that anti-TNF- mAbs produced specific modulating effects on the immune system without rendering the animals immune-compromised.[23]

Golimumab was approved in 2009 in both the US and Europe for the treatment of moderate to severe RA, Psoriatic Arthritis (PsA), and Ankylosing Spondylitis (AS).[24] In 2013, golimumab was approved for the treatment of Ulcerative Colitis (UC) and in 2016 for the treatment of Juvenile Idiopathic Arthritis (JIA).

Golimumab is available in subcutaneous (SC) or intravenous (IV) forms. Huffstutter concluded that improvements in disease activity were comparable in SC and IV administration forms, with no apparent benefit from switching from SC to IV.[25]

Golimumab is available as a 0.5 ml (50 mg golimumab) or 1 ml (100 mg golimumab) solution.[16,21] For RA, PsA, AS or

nonradiographic axial Spondyloarthritis (nr-axSpA), the indicated dosing is a 50 mg SC injection once a month. There was no clear evidence of improved American College of Rheumatology (ACR) or Ankylosing Spondylitis Assessment Study (ASAS) response with higher dose (100 mg) compared to lower dose (50 mg) for those indications. Regarding safety, in some studies, the association MTX + golimumab 100 mg had more frequent adverse events than the lower dose. .[26–30] Kay et al[31] assessed safety of golimumab by pooling data from five pivotal phase III trials in patients with active RA, PsA or AS. Each study included a placebo-controlled phase, followed by uncontrolled study periods up to week 160, during which all patients received golimumab 50 or 100 mg. The incidence of serious infections observed with placebo was higher (5.31/100 patient-years) than with golimumab 100 mg (5.09/100 patient-years) or golimumab 50 mg (3.03/100 patient-years). For UC, golimumab approved dose is 200 mg SC (two 100-mg injections) on the first day of treatment, followed by one 100-mg injection 2 weeks later, then maintenance with 100 mg SC every 4 weeks (q4w). In UC studies, there was a trend toward a dose–response relationship. .[32,33] In children with JIA, with body weight less than 40 kg, the indicated dosing is 30 mg/m2 of the body surface area. The 50 mg administered once a month is indicated for children with a body weight of at least 40 kg.[34]

Pharmacokinetics

pharmacokinetics and immunogenicity. Median, two distinct receptors for TNF alpha are known (TNFR1 and TNFR2), and activation of these receptors by TNF alpha induces an intracellular signaling cascade, with effects involving cytokine secretion, cell proliferation, and apoptosis. In particular, activation of TNFR1 (especially with soluble TNF) activates the nuclear factor-kappa B receptor (NFKB), which translocates to the nucleus and activates the transcription of several pro-inflammatory cytokine genes, such as IL-8, IL-1, IL-6, COX-2, and TNF alpha.[9]

Pharmacokinetics may be influenced by disease type or severity, body weight, immunogenicity, and the concomitant use of other medications such as methotrexate (MTX).[4]

The exact metabolic pathway of golimumab is unknown.

The pharmacokinetic (PK) characteristics of golimumab have been evaluated after a single IV administration in patients with RA[35] and a single SC or IV administration in healthy subjects.[36] Following a 30-min IV infusion, serum golimumab concentration exhibited a typical biphasic PK profile with a rapid distribution phase and a slow elimination phase. After a single SC administration of golimumab 100 mg in healthy subjects, golimumab was absorbed slowly into the blood with a median time to reach maximum serum concentration (Tmax) of 4.0 days.[36] Following SC administration of 50 mg golimumab, the Tmax ranges from 2 to 6 days, with a mean concentration (Cmax) of approximately 3.1 ± 1.4 μg/ml.[37]

The median half-life (t1/2) appeared to increase with an increase in dose.[35] The t1/2 after SC was consistent with that observed after IV administration.[36] The t1/2 was estimated to be about 2 weeks either in healthy subjects or in patients with active RA, PsA, or AS.[37]

The mean maximum concentration (Cmax) and mean area under the concentration (AUC) also increased in a dose-proportional manner. RA, PsA, and AS patients treated with concomitant MTX had higher mean steady-state trough concentrations compared with those treated without concomitant MTX.[38]

The mean clearance (CL) after IV administration of golimumab seemed to be independent of dose,[35] but in patients with RA, the concomitant use of MTX reduced the apparent clearance of golimumab.[38]

The volume of distribution at steady state (Vss) was estimated as the sum of volume of distribution in the central compartment (Vc) and volume of distribution in the peripheral compartment (Vp). However, the volume of distribution of golimumab was approximately twice the plasma volume, which suggests that golimumab is located primarily in the circulatory system and has also some extravascular tissue distribution.[36]

Body weight was identified as a significant covariate for Vc, but the clinical relevance of this relationship shouldn't be important.

As said before, t1/2 were similar following SC and IV administrations, indicating that the administration route did not affect the elimination of golimumab. Concentration-time curves during the elimination phase following SC or IV administration of golimumab were almost parallel.[36]

The mean absolute bioavailability of golimumab is comparable to those for other monoclonal antibodies delivered subcutaneously. The basis for the 50–60% bioavailability of protein drugs after SC injection is not known, but the degradation/metabolism at the site of injection or during the transport through the lymphatic system is associated with their presystemic loss.[36]

The use of different anatomical regions for the administration of SC injections have been shown to influence the absorption of protein drugs like insulin. However, Xu et al[36] showed that the PK parameters including absorption parameters (Cmax, Tmax, and bioavailability) of SC golimumab appeared to be unaffected by injection sites (upper arm, abdomen, and thigh). Possibly, the inherent slow absorption of monoclonal antibodies likely makes the regional variation of lymph flow negligible.[36]

Immunoglobulins are eliminated by two main mechanisms: one is cellular uptake followed by intracellular catabolism and the other is thought to be by binding to its target antigen leading to an elimination of the complex by the immune system.[34]

Immunogenicity of golimumab

Biologic immunogenicity differs among agents. High level of immunogenicity are associated with increased risk of secondary loss of response to biologics.[39] Thomas et al.[19] documented in a systematic review on the immunogenicity of TNF inhibitors that golimumab was one of the least immunogenic.

Immunogenicity is assessed by the detection of ADAs that specifically bind to the biologic drug.[40] The drug-ADA complexes interfere with drug binding to TNF, leading to hypersensitivity, a higher risk of injection site or infusion reactions, an increase in drug clearance and loss of response. .[41]

Several phase 3, randomized, double-blind, controlled, parallel-group studies were conducted to evaluate the efficacy and safety of golimumab therapy. In the GO-VIBRANT[42] study, antibodies to golimumab were detected in 44 (19.5%) of golimumab-treated patients after IV administration of golimumab at 2 mg/kg through week 20. Antibody titers were generally low in these patients (39 of these patients had titers below 1:100) and had no apparent effect on efficacy or safety, although median golimumab concentrations were generally lower in patients who tested positive for antibodies to golimumab, with golimumab concentrations decreasing as peak titers increased. GO-FORWARD, [27] GO-REVEAL[30] and GO-RAISE studies[29] aimed to evaluate the efficacy and safety of SC golimumab therapy (50 and/or 100 mg q4w with or without concomitant MTX). In the GO-FORWARD study[27] 5 of 236 patients with available samples (2.1%) had antibodies to golimumab at week 24. All the patients were in the group that was on golimumab 100 mg injections plus placebo. The observed incidence of antibodies to golimumab was too low to evaluate their effect on clinical efficacy and safety. In the GO-REVEAL[30] and GO-RAISE studies, [29] the incidence of antibodies to golimumab was low (4.6% and 4.1% of patients, respectively) and had no apparent impact on ACR responses or injection-site reactions. No patient receiving MTX at baseline developed antibodies to golimumab.

Serum samples previously tested via the original enzyme immunoassays (EIA) from the GO-FORWARD, GO-REVEAL, and GO-RAISE studies, were re-analyzed using the novel highly sensitive drug-tolerance EIA (DT-EIA) to determine the presence of antibodies to golimumab. DT-EIA could also detect ADA bound in an immune complex with the drug. Samples were collected at week 0, week 24 and week 52 and at any unscheduled time point. Immunogenicity results were evaluated and compared between methods. Overall, 31.7% (DT-EIA) vs 4.1% (original EIA) of patients were ADA+.

Patients with higher ADA titers generally had lower serum golimumab concentrations over time than patients with lower peak titers. However, the detection of these ADA did not change the clinical response.[40]

Identical comparison was done in a series of trials evaluating the efficacy and safety of golimumab compared to placebo, in biologics naïve (BN) patients with moderate-to-severe UC: PURSUIT-IV, [43] PURSUIT-SC, [32] and PURSUIT-M .[33] Median ADA titers with the DT-EIA method were higher among those classified as positive with the original EIA method. The newly positive patients mainly had low ADA titers with the DT-EIA. Patients with higher ADA titers generally had lower serum golimumab concentrations. With the DT-EIA no effects of positive ADA status were observed at week 6 on clinical response, clinical remission, or mucosal healing in PURSUIT-IV or PURSUIT-SC. Although the development of golimumab ADAs did not preclude clinical efficacy, a trend toward decreased efficacy in ADA-positive patients was observed compared with ADA-negative patients in PURSUIT-M. In the original EIA assessment, efficacy was lower among ADA-positive and ADA-negative patients compared with those in whom ADAs were not identified. The fact that in the original EIA both ADA-positive and ADA-negative patients had no detectable golimumab in their samples suggests that the most important predictor of efficacy is the level of golimumab drug concentration instead of the presence of antibodies.[41]

Clinical efficacy

The clinical efficacy of golimumab in inflammatory immune diseases has been shown in a series of phase III trials.

The efficacy of SC golimumab administered every 4 weeks was investigated in randomized, double-blind, placebo-controlled, multicenter, phase III trials in patients with RA, PsA, AS, nr-axSpA, JIA and UC Table 1.

Rheumatoid arthritis

The GO-BEFORE, [26] GO-FORWARD[27] and GO-AFTER[28] Table 1 studies evaluated adults with RA diagnosed according to ACR criteria and active disease [at least 4 swollen joint counts (SJC) and 4 tender joint counts (TJC)]. In the first two studies' participants also met at least 2 of the following criteria: c-reactive protein (CRP) >1.5 mg/dL; erythrocyte sedimentation rate (ESR) >28 mm/h; >30 min of morning stiffness; bone erosion [determined by radiography and/or Magnetic resonance imaging (MRI)]; anti-cyclic citrullinated peptide antibody-positive; rheumatoid factor-positive.

GO BEFORE was a multicenter phase III trial, in which patients were MTX and TNFi-naïve. Six hundred and thirty-seven patients were randomized to receive placebo plus MTX (group 1), golimumab 100 mg plus placebo (group 2), golimumab 50 mg plus MTX (group 3), or golimumab 100 mg plus MTX (group 4). The primary endpoint was the difference in the ACR50 response at week 24 between groups 3 and 4 combined versus group 1. Although the primary endpoint was not achieved (38.4% vs 29.4%, $p = .053$), the combination of golimumab plus MTX demonstrated a significantly better response compared with placebo plus MTX in other efficacy parameters: 34.8% of patients in group 3 ($p = .010$) and 41.1% of patients in group 4 ($p < .001$) achieved at least 20% improvement in the ACR response (ACR20) at week 4 compared with 21.9% of patients in group 1; greater proportions of patients in group 3 (61.6%) and group 4 (61.6%) achieved ACR20 at week 24 compared with group 1 (49.4%; $p = .028$ for both); the proportion of patients achieving a Disease Activity Score in 28 joints (DAS28) response at week 24 was significantly higher in group 3 (73%; $p = .027$) and group 4 (76.7%; $p = .003$) compared with group 1 (61.3%).

Patients enrolled in GO-FORWARD[27] had active disease despite current MTX therapy. This was a phase III, multicentre, randomized, double-blind, placebo-controlled trial. Patients were randomly assigned in a 3: 3: 2: 2 ratio to receive placebo plus MTX (group 1, n = 133), golimumab 100 mg plus placebo (group 2, n = 133), golimumab 50 mg plus MTX (group 3, n = 89), or golimumab 100 mg plus MTX (group 4, n = 89). The co-primary endpoints were the ACR20 at week 14 and the change from baseline in the health assessment questionnaire-disability index (HAQ-DI) score at week 24.

The addition of golimumab injections q4w to MTX in patients with active RA significantly reduced the signs and symptoms of RA: 33% of patients in group 1 achieved an ACR20 response at week 14, compared with 55.6% ($p < .001$)

Table 1. Selected phase III trials of golimumab that were important to indications approval.

Study	Acronym	Disease	Study arms	Patients randomized (n)	Primary Endpoint/ efficacy	Safety issues
Emery P, et al[26]	GO-BEFORE	RA	Placebo +MTX (group 1), GOL100 mg +placebo (group 2), GOL 50 mg +MTX (group 3), GOL 100 mg+MTX (group 4)	637	Not achieved. Week 24: ACR50 showed no differences; DAS28 response and DAS28 remission in the groups 3 + 4 vs group 1 were significant	At week 24, 72.5%, 68.2%, 81.6% and 76.1% of patients reported AE in groups 1,2,3 and 4, respectively. SAE were reported in 6.9%, 3.2%, 6.3% and 6.3% in the same groups.
Keystone EC, et al[27]	GO-FORWARD	RA	Placebo +MTX (group 1), GOL 100 mg +placebo (group 2), GOL 50 mg +MTX (group 3), GOL 100 mg +MTX (group 4)	444	Achieved; Week 14: ACR20 was statistically superior in the groups 3 and 4 vs group 1	During the placebo-controlled phase of the study, 60.9%, 63.2%, 68.5% and 69.7% of patients reported AE in groups 1,2,3 and 4, respectively. After early scape, SAE reported in group 4 was 12.4% vs 3.7%, 6% and 4.2% in groups 1, 2 and 3
Smolen J, et al[28]	GO-AFTER	RA	Placebo, GOL 50 mg, GOL 100 mg	461	Achieved; Week 14: ACR20 was statistically higher in the GOL groups vs placebo	Weeks 1–16: AE were recorded in 70% patients on placebo, 61% on 50 mg GOL, and 73% on 100 mg GOL. Weeks 1–24, SAE were recorded in 10% of patients on placebo, 5% on 50 mg GOL, and 4% on 100 mg GOL.
Kavanaugh A, et al[30]	GO-REVEAL	PsA	Placebo, GOL 50 mg, GOL100 mg	405	Achieved; Week 14: ACR20 in the GOL groups was statistically superior than that of group placebo	Weeks 1–16, AE were recorded in 59% patients on placebo, 68% on 50 mg GOL and 65% on 100 mg GOL. Weeks 1–24, SAE were recorded in 6% patients on placebo, 2% on 50 mg GOL, and 3% on 100 mg GOL.
Kavanaugh A, et al[42]	GO-VIBRANT	PsA	Placebo, IV GOL at 2 mg/kg	480	Achieved; Week 14: ACR20 in the GOL group was statistically superior than that of group placebo	week 24: AE were reported in 46.3% of patients in the GOL group (of which 2.9% were SAE) vs 40.6% in the placebo group (of which 3.3% were SAE)
Inman R. et al[29]	GO-RAISE	SpA	Placebo, GOL 50 mg, GOL 100 mg	356	Achieved; Week 14: ASAS20 in the GOL groups was statistically superior than that of group placebo	week 24:AE reported in 85.6% of patients in the GOL group (of which 5.4% were SAE) vs 76.6% in the placebo group (of which 6.5% were SAE)
Sieper J. et al[44]	-	nr-axSpA	Placebo, GOL 50 mg	198	Achieved; Week 16: ASAS20 in the GOL group was statistically superior than that of group placebo	week 16:AE reported in 41.2% of patients in the GOL group (of which 1% were SAE) vs 47% in the placebo group (of which 2% were SAE)
Brunner H. et al[45]	GO-KIDS	JIA	Part 1 GOL (30 mg/m^2; maximum: 50 mg/dose) and MTX Part 2: GOL or placebo; Part 3: GOL continued or restarted as in Part 1.	173	Not achieved; Part 2: treatment groups had comparable JIA flare rates; After Part 1, JIA ACR30 was achieved by 89.0% of patients	During Part 2, AE were reported in 78.2%of patients in the GOL group (of which 10.3% were SAE) vs 82.9% in the placebo group (of which 13.2% were SAE)
Sandborn, WJ et al[32]	PURSUIT–SC*	UC	Phase 2: Placebo, GOL100/50 mg, 200/100 mg, 400/200 mg Phase 3: Placebo, GOL 200/100 mg, 400/200 mg	1065	Achieved; Week 6: more patients in the treatment groups achieved clinical response compared with the placebo arm	AE reported in 37.5%, 38.9%, and 38.2% for the 200/100 mg GOL 400/200 mg GOL and placebo arms, respectively. SAE reported by 3% of GOL-treated and 6.1% of placebo-treated patients.
Rutgeerts P. et al[43]	PURSUIT–IV*	UC	Phase 2: placebo, GOL 1 mg/kg, GOL 2 mg/kg, GOL 4 mg/kg Phase 3: placebo, GOL 2 mg/kg,GOL 4 mg/kg	291	Not achieved; Efficacy with golimumab IV induction was lower than expected	Week 6: AE reported in 36.6% of GOL treated patients and 31.2% of patients given placebo; SAE were reported in 3.8% and 2.6%, respectively
Sandborn, WJ et al[33]	PURSUIT–M	UC	Placebo, GOL50 mg, GOL100 mg	464	Achieved; Week 54: the proportions of patients who maintained a clinical response was significantly greater in GOL compared with the placebo group	Week 54: AE were reported in 66% given placebo (of which 7.7% were SAE), 72.7%, given 50 mg GOL (of which 8.4% were SAE) and 73.4% given 100 mg GOL (of which 14.3% were SAE)

* Phase 2/3 induction study

Note: Golimumab: GOL; RA: Rheumatoid Arthritis; PsA: Psoriatic Arthritis; AS: Ankylosing Spondylitis; nr-axSpA: Nonradiographic axial Spondyloarthritis; JIA: Juvenile Idiopathic Arthritis; UC: Ulcerative Colitis; Adverse events: AE; SAE: serious adverse events; ACR20: at least 20% improvement in the American College of Rheumatology criteria; ASAS20: at least 20% improvement in the Assessment in AS

in the combined groups 3 and 4. At week 24, patients in the combined groups 3 and 4, also improved physical function [median improvement in HAQ-DI score was −0.44 ($p < .001$) compared with −0.13 in group 1].

In the GO AFTER study, patients had active disease after discontinuing previous TNFi therapy because of lack of effectiveness or other reasons, despite any ongoing treatment [conventional disease-modifying antirheumatic drugs (csDMARDs), oral corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs)]. Four hundred and sixty one patients were randomized to receive placebo, 50 mg golimumab, or 100 mg golimumab. The primary endpoint was achievement of ACR20 at week 14. At week 16, patients who had less than 20% improvement in tender and swollen joint counts were given rescue therapy and changed treatment from placebo to 50 mg golimumab, or from 50 mg to 100 mg golimumab. At week 14, 54 (35%) patients on 50 mg golimumab ($p = .0006$), and 58 (38%) patients on 100 mg golimumab ($p = .0001$) achieved ACR20. In this study, golimumab showed efficacy in RA patients with active disease who had previously received one or more TNFi.[28]

GO-SAVE[46] was a multicenter, assessor-blinded study, where 433 patients with active RA despite MTX and past adalimumab/etanercept treatment received open-label SC golimumab 50 mg q4w. Week 16 responders continued therapy through week 52 and nonresponders were randomized (1:2) to double-blind SC golimumab 50 mg q4w or IV golimumab 2 mg/kg (weeks 16, 20, every 8 weeks). The primary endpoint (ACR20) was achieved by 151 of 433 patients (34.9%) at week 14, even after having failed treatment with etanercept, adalimumab, or both.

The combined evidence obtained in these trials have shown that golimumab 50 mg every month is effective in the treatment of active RA patients after failure of conventional or biological DMARDs.

Psoriatic arthritis

Unlike csDMARDs, TNFi have been demonstrated to prevent the radiographic progression of PsA.[4] GO-REVEAL[30] and GO-VIBRANT[42] are the two major randomized clinical phase III studies testing the use of golimumab in PsA Table 1. Both showed efficacy of golimumab in the SC and IV form, respectively.

In the GO-REVEAL study, treatment of PsA showed clinical efficacy, including ACR20, DAS28 response, ≥75% improvement in Psoriasis Area and Severity Index (PASI75) scores, PsA-modified Sharp/van der Heijde scores (SHSs) and physical function, which was maintained over the period of study.[30,42,47,48] Adults with active PsA (≥3 SJC and TJC, active psoriasis) were randomly assigned to SC placebo, golimumab 50 mg, or golimumab 100 mg every q4w. All patients received golimumab 50 mg or 100 mg from week 24 onward. MTX was also taken by approximately half of the patients. Golimumab was effective in maintaining clinical improvement throughout year-5[48] (ACR20: 62.8–69.9%, DAS28: 75.2–84.9% for randomized patients; PASI75: 60.8–72.2% among randomized patients with ≥3% body surface area involvement) and inhibiting radiographic progression (mean changes in PsA-modified SHS: 0.1–0.3) among patients with radiographic data.

GO-VIBRANT[42] was a phase III, randomized, double-blind, placebo-controlled trial, in which patients were randomly assigned to receive IV placebo or golimumab 2 mg/kg at weeks 0, 4, 12, and 20. The primary endpoint was the proportion of patients achieving an ACR20 response at week 14. Secondary endpoints included ACR50 and ACR70 responses, a PASI75 response at week 14, change from baseline in HAQ DI score at week 14 and change from baseline at week 24 in the SHSs. Patients selected had active PsA (defined as ≥5 of 66 SJC and ≥5 TJC at screening and baseline and a high-sensitivity CRP level of ≥0.6 mg/dl at screening) despite csDMARD therapy and/or NSAID therapy or demonstrated intolerance to these agents. Previous biologic therapy was not allowed. At week 14, 75.1% of patients in the golimumab group achieved an ACR20 response (primary endpoint) compared with 21.8% in the placebo group ($p < .001$). All major secondary endpoints were achieved. Also, patients in the golimumab group had less radiographic progression than those in the placebo group ($p < .001$).

GO-DACT was a phase 3b randomized, double-blind, placebo-controlled trial of golimumab plus MTX versus placebo plus MTX testing the improvement in dactylitis in MTX-naïve patients with PsA. The primary endpoint was Dactylitis Severity Score (DSS) change from baseline to week 24. Forty-four patients were randomized: 21 received golimumab plus MTX and 23 placebo plus MTX for 24 weeks. Patients treated with golimumab plus MTX exhibited significantly greater improvements in DSS relative to MTX monotherapy (median change of 5 vs 2 points, respectively; $p = .026$) at week 24. Higher proportions of patients achieved at least 50% or 70% improvement in DSS ($p < .005$) and 20% ($p < .05$), 50% ($p < .001$), or 70% ($p < .05$) improvement in Leeds Dactylitis Index (LDI) in the golimumab plus MTX group. According to Vieira-Sousa et al, the combination of golimumab plus MTX is associated with significantly higher clinical improvements in dactylitis in comparison with MTX monotherapy.[49]

Ankylosing spondylitis

Accordingly to a Cochrane meta-analysis of 18 randomized clinical trial (RCTs), patients with AS treated with TNFi (except for certolizumab) were significantly more likely to achieve an ASAS40 response at 6 months compared with placebo. .[50]

In the GO-RAISE study, [29] patients with active AS, a Bath AS Disease Activity Index (BASDAI) score >4, and a back pain score of >4 were assigned in a 1.8:1.8:1 ratio to receive SC injections of golimumab (50 mg or 100 mg) or placebo every 4 weeks. The primary endpoint was the proportion of patients achieving at least 20% improvement in the Assessment in AS (ASAS20) criteria at week 14. Significantly, more golimumab-treated patients achieved an ASAS20 response compared with patients in the placebo group ($p < .001$) Table 1. Patients receiving golimumab also showed significant improvement in the BASDAI score and in the Bath AS Functional Index (BASFI) score ($p < .001$).

Mok et al[51] aimed to compare the effect of golimumab and pamidronate on clinical efficacy and MRI inflammation in AS. Eligible patients [ASAS criteria for AS and active disease (BASDAI score ≥ 4] were randomized in a 2:1 ratio to receive golimumab (50 mg subcutaneously) or pamidronate (60 mg intravenously) q4w for 48 weeks. Thirty patients were recruited. Pamidronate was associated with improvement in patient-reported outcomes (PRO) and ASAS20 and ASAS40 response rates were similar, however, golimumab was effective in reducing the levels of inflammatory markers (ESR and CRP), BASDAI, BASFI, Ankylosing Spondylitis Disease Activity Score (ASDAS), and MRI inflammation of the spine and sacroiliac joints.

Nonradiographic axial SpA

A phase III, double-blind, randomized, placebo-controlled trial was performed to evaluate SC golimumab (50 mg) versus placebo in patients aged 18–45 years who had active nr-axSpA according to the ASAS criteria.[44] It was also necessary to have high disease activity and an inadequate response/intolerance to NSAIDs. Of the 198 randomized patients, 97 received golimumab and 100 received placebo subcutaneously q4w. The primary endpoint was an ASAS20 response at week 16 and this was achieved by significantly more patients in the golimumab group than in the placebo group (71.1% versus 40.0%; $p < .0001$). Table 1

In patients who had a positive MRI or an increased CRP at treatment start, the effect on ASAS20 and ASAS40 responses was superior.[44,52]

Juvenile idiopathic arthritis

GO-KIDS[45] was a three-part randomized, double-blind, placebo-controlled, withdrawal study in which 173 children (aged 2–17 years) participated. Participants had active polyarticular juvenile idiopathic arthritis (pJIA), ≥5 active joints, and an inadequate response to MTX. Those patients received open-label golimumab (30 mg/m2 of body surface area; maximum: 50 mg/dose) q4w together with weekly MTX during Part 1 (weeks 0–16). Patients with at least 30% improvement in the American College of Rheumatology Criteria for JIA (JIA ACR30) were included in the double-blinded Part 2 (weeks 16–48) after 1:1 randomization to continue golimumab or start placebo. In Part 3, golimumab was continued or could be restarted as in Part 1. Eighty nine percent (154/173) had a JIA ACR30 response. Treatment with golimumab in children with active pJIA resulted in a rapid clinically meaningful improvement that was maintained over time Table 1.

Ulcerative colitis

Studies leading to the approval of golimumab for UC were included in the "Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment" (PURSUIT) and included trials that evaluated the efficacy and overall safety of golimumab compared to placebo, in BN patients with moderate-to-severe UC Table 1.[53]

Studies were divided into two phases: induction (PURSUIT–SC) and maintenance (PURSUIT-M.)

PURSUIT-SC[32] was the first trial evaluating golimumab induction therapy via the SC route. It was a multicenter, randomized, double-blind, placebo-controlled trial. Data showed significantly higher clinical response rate and mucosal healing for both golimumab induction regimens selected (400/200 mg and 200/100 mg) when compared to placebo in the 6-week time of observation. In phase 2 study, 169 patients were randomized to receive either placebo or different regimens of golimumab at week 0 and week 2: 100/50 mg; 200/100 mg; 400/200 mg. After analysis of the dose-finding data, the 400/200 mg and 200/100 mg regimens were selected for the phase 3 study (774 patients). In this phase 2/3 induction study, golimumab treatment was associated with a higher level of clinical response, clinical remission, mucosal healing, and improved quality of life, as compared with placebo.

PURSUIT-IV[43] was a trial with the same eligibility criteria, evaluating the efficacy of a single IV induction dose. This route of administration did not reach primary clinical end points at week 6 and the study enrollment was stopped because of unsatisfactory results.

The IV route was associated with a higher peak concentration; however, this was not relevant for the long-period efficacy. In the SC induction regimen there was a more constant serum drug concentration during the 6-week induction regimen and had better results.

The maintenance study, PURSUIT-M[33] was a multicenter, randomized, placebo-controlled study, in which patients who completed golimumab induction trials were randomly assigned to placebo or 50 or 100 mg golimumab groups, every 4 weeks throughout week 52. Patients who responded to placebo in the induction study continued to receive a placebo. Nonresponders in the induction study received 100 mg golimumab. The primary endpoint was clinical response maintained throughout week 54 and secondary endpoints included clinical remission and mucosal healing at weeks 30 and 54. Clinical response was maintained through week 54 in 47.0% of patients receiving 50 mg golimumab and 49.7% of patients receiving 100 mg golimumab (compared with 31.2% of the patients included in the placebo group). At weeks 30 and 54, a higher percentage of patients who received 100 mg golimumab were in clinical remission and had mucosal healing (27.8% and 42.4%) as compared with patients given placebo (15.6% and 26.6%, respectively) or 50 mg golimumab (23.2% and 41.7%, respectively).

In 2017, Japanese authors published the PURSUIT-J,[54] a double-blind randomized placebo-controlled trial, with similar results in long-term efficacy (56.3% vs 49.7% of PURSUIT-M) at week 52 in a Japanese cohort of UC BN patients.

Although only a few real-life studies support efficacy of golimumab in biologics experienced (BE) patients, it seems to be an alternative treatment even in previously experienced TNFi UC patients.[55, 56, 57, 58, 59] Only the patients who received golimumab after the previous failure of 2 TNFi had significantly worse outcomes.[59]

Golimumab was shown to be effective and is also approved for administration in children with UC.[60]

Crohn's disease

No formal trial has been performed to assess the efficacy of golimumab in Crohn's disease (CD). This may be due to a large

number of reasons, including strategical considerations by the manufacturer and regulatory issues.[61] A retrospective observational study conducted in 45 CD BE patients (97.7% had experienced two other TNFi) demonstrated optimal clinical response (71.1% at 6 months, 70.9% at 12 months).[62] Russi et all[61] performed a retrospective study of a case series of 8 refractory CD patients receiving golimumab as an off-label rescue therapy. All patients were previous anti-TNF nonresponders to at least 1 agent. Clinical response was observed in 3 patients. Although the study was small, there seem to be promising results for refractory CD patients.

Its efficacy was also evaluated in a retrospective study[63] where 115 CD patients, who had already been on 2 biological therapies before, started therapy with golimumab. After 4 months of treatment, clinical response was achieved in 55.8% of cases. The probability of maintaining the therapy without escalation at 6 and 12 months was 54.6% and 34.9%, respectively. The maintenance dose scheme was the same as that used for UC for most of the patients (only 1.9% received > 100 mg/4 weeks) and no serious adverse events were reported. Lack of CRP in all patients and of endoscopic data were limitations of this study.

Randomized prospective trials with a higher number of patients are needed to confirm these data and to establish the optimal dosing regimen. Initial conclusions based on the studies reported above suggests efficacy in TNFi-resistant CD patients.

Uveitis

No formal trial has been performed to assess the efficacy of golimumab in uveitis.

Palmou-Fontana et al[64] evaluated the efficacy of golimumab in a multicentre study of JIA-associated uveitis refractory to csDMARD and to other TNFi agents. Seven patients (5 females; mean age 21.7 ± 7.5 years) were eligible and initiated golimumab 50 mg q4w. Besides corticosteroids and csDMARDs, patients had received a median of 2 biologic agents (range 0–3) including adalimumab (n = 6), etanercept (n = 2), infliximab (n = 3) and abatacept (n = 2). Complete remission of uveitis was achieved in 4 of 7 patients after 16.8 ± 11.4 months of follow-up.

Tosi et al[65] pretended to show the efficacy of golimumab and certolizumab for the treatment of uveitis. Twenty-one patients were enrolled in the study, 10 patients were treated with golimumab. There were cases of anterior, intermediate, posterior uveitis and even panuveitis. Twelve months after the beginning of golimumab a significant reduction in ocular flares was observed.

Psoriasis

No formal trial has been performed to assess the efficacy of golimumab in psoriasis. However, the GO-REVEAL trial[30] also demonstrated efficacy for treating psoriasis as measured by PASI responses. Forty percent of the patients in the golimumab 50 mg group and 58% of those in the golimumab 100 mg group had a PASI75 at week 14 (major secondary end point), compared with 3% of placebo-treated patients ($p < .001$ for both doses). Golimumab was also effective in treating nail disease, with a significant improvement observed for the NAPSI, the physician's global assessment of psoriatic nail disease. Efficacy was maintained after 5 years.[48]

Safety

The risks and adverse events associated with the use of golimumab are generally similar to those of the other TNFi Table 1. Singh et al [66, 70, 91, 92] found no statistically differences between golimumab and placebo regarding adverse events, including infections or cancer.

Allergic reactions are rare. The needle cover as well as the syringe in the autoinjector contains dry natural rubber (a derivative of latex) and should not be handled by individuals who are sensitive to latex.[67]

Although demyelinating disorders were reported infrequently among patients treated with golimumab, [62] TNF antagonism may be associated with demyelinating disease and that is why all TNFi should be avoided in patients with demyelinating disorders such as multiple sclerosis.

Pneumonia and soft-tissue infections are the most common serious infections observed among patients on TNFi .[11] Kay et al studies[31, 68] serious infections appeared to be more frequent among golimumab-treated patients with RA (9.1%) than among golimumab-treated patients with PsA (2.5%) or AS (4.8%). The literature on TNFi in the treatment of RA contains more data to suggest an increased frequency of infections; however, the same level of vigilance for infections is advised regardless of indication.[11] Serious infections also appeared to be more common among patients for whom oral corticosteroid use was present at baseline.[31,68] An increased risk of tuberculosis (TB) among patients receiving TNFi has been observed, and several meta-analyses have evaluated the risk of TB in patients treated with TNFi. TNF plays an essential role in host defense against TB, including granuloma formation and containment of the disease. The overall incidence of TB in patients with rheumatic diseases who are treated with TNFi varies by disease, population and the specific TNFi used.[69, 71] In one registry series for golimumab, the TB incidence was similar to adalimumab.[72] Ai et al[73] analyzed the TB risk in patients with RA treated with TNFi in 50 published RCT. For golimumab the risk ratio (RR) was 1.18, compared with a RR for infliximab, adalimumab and certolizumab pegol of 1.65, 1.01, and 1.02, respectively. In the golimumab safety update, [31,68] the TB incidence was numerically higher with golimumab 100 mg than with golimumab 50 mg at week 160, however, not higher than placebo.

Due to the potential of TNFi to cause reactivation of latent tuberculosis, screening is recommended for all patients. When TB treatment is indicated, it is necessary two months of TB treatment in active tuberculosis cases and one month in latent tuberculosis infection before the beginning of TNFi therapy.[74]

Serological tests for the Hepatitis C Virus (HCV), Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV) should be obtained before starting TNFi therapy. In patients with chronic viral infections, the appropriateness of TNFi therapy should be discussed.[75]

The pneumococcal vaccine is recommended before TNFi initiation, as well as the yearly influenza vaccine.[74, 75]

As for other biologics, live vaccines should not be used during treatment with golimumab.[75]

Approximately 25% of patients treated with TNFi develop cutaneous adverse events, (usually months to years after initiating treatment), including xerosis cutis, eczema (often psoriasiform), psoriasis, palmoplantar pustulosis, cutaneous infections, and alopecia. There are rare reports of paradoxical triggering of psoriasis in new locations, particularly pustular lesions of the palms in patients with PsA treated with TNFi. The typical skin lesion is an orange-red psoriasiform eczema affecting the flexures, genitalia, scalp, or face, with high susceptibility to bacterial superinfection with *Staphylococcus aureus*. Only rarely the discontinuation of TNFi is necessary, if adequate dermatological treatment is administered.[76]

The overall incidence of malignancy did not appear to be increased with golimumab vs placebo or when compared with rates expected in the general population.[68]

In the meta-analysis (MA) by Le Blay et al[77] no increased risk of all types of malignancy with the use of golimumab was found. Michaud et al[78] did a MA update of 44 RCT to evaluate the safety data of TNFi in RA patients. Studies evaluated adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab. The risk of malignancy in patients treated with TNFi as a group or individually was not significantly different from those treated with placebo or csDMARDs in the control group. Also, Moulis et al[79] excluded an excess cancer risk of the five TNFi compared with placebo in RA patients.

Lemaitre et al[80] evaluated the risk of lymphoma in IBD patients exposed to thiopurine or anti-TNF therapy, using data from a large observational cohort study of French patients. Compared with exposure to neither medication, the risk of lymphoma (either Hodgkin lymphoma or non-Hodgkin lymphoma) was higher among those exposed to combination therapy (Adjusted Hazard Ratios (aHR), 6.11; 95% CI, 3.46–10.8; $p < .001$), followed by thiopurine monotherapy [aHR, 2.60; 95% Confidence Intervals (CI), 1.96–3.44; $p < .001$] and anti-TNF monotherapy (aHR, 2.41; 95% CI, 1.60–3.64; $p < .001$).

An increased risk of malignancy has been shown in multiple studies with thiopurines in IBD patients and the majority of antiTNF–treated patients are either current or past users of thiopurines. Thus, the relative risk of malignancy with anti-TNF monotherapy in IBD is not clear. Osterman et al[81] concluded by a meta-analysis that although the use of adalimumab in combination with an immunomodulator carried an increased risk for malignancies, the use of anti-TNF monotherapy did not have a greater incidence of cancer. The TREAT registry[82] allowed to assess the potential associations between malignancy and antiTNF therapy in patients with CD. Treatment with IFX alone (OR 1.96; 95% CI 0.23–17.02; $p = .54$) was associated with lower risk of malignancy than the use of immunosuppressives alone (OR 4.19; 95% CI 0.58–-30.37; $p = .16$) or with combination therapy (OR 3.33; 95% CI 0.46–24.06; $p = .23$). A rare form of lymphoma, hepatosplenic T cell lymphoma, has been reported in patients receiving combination therapy with antiTNF and azathioprine. However, hepatosplenic T cell lymphoma have also occurred in patients receiving azathioprine alone.[83] Colombel et al[84] evaluated the safety of infliximab and azathioprine therapy alone or in combination for CD and the incidence of adverse events was similar. According to these data, we cannot exclude that the risk of malignancy with TNFi in IBD patients can be driven just by the use of thiopurines.[85]

Bongartz et al[86] and Askling et al[87] studies demonstrated an increased risk of malignancies in patients treated with TNFi. However, they did not include golimumab in their studies.

Although there is no evident risk of malignancies associated with golimumab in current scientific literature, [88] a risk-benefit evaluation should be done.

No association has been found between TNFi given during pregnancy and birth defects, or an increased incidence of adverse pregnancy outcomes. However, published evidence is limited and consists mostly of case reports and case series.[89] Based on the analysis of the PIANO data there was no increase in the rate of birth defects, infections, achievement of developmental milestones at 1 year, height or weight. However, there was an increase in any complication [odds ratio (OR) 1.7 (1.0–2.2)] and preterm birth [OR 2.4 (1.3–4.3)] in the combination therapy group compared with the unexposed.[89]

Data from the health registries in Denmark and Sweden suggested that women who received TNFi agents during pregnancy had a slightly higher risk of having children with birth defects. In this study, only 4 women were specifically taking golimumab and reported no adverse events during pregnancy.[90]

After the second semester of pregnancy there is an increased placental transfer of monoclonal antibodies via the neonatal Fc receptor. Golimumab, as a complete IgG1 antibody, crosses the placenta and can be detected for up to 6 months in the serum of the infant born from a treated woman. Consequently, these infants may be at increased risk of infection.[91, 92]

The timing of anti-TNF dosing during pregnancy is still debated. The concern with stopping the anti-TNF early is the possibility of disease flare, which may lead to preterm birth, as well as immunizing the mother to the drug. In the patient in remission, some authors have suggested discontinuing anti-TNF agents at week 20 of gestation to reduce the amount of drug present in the infant at birth. In the patient with active disease, anti-TNFs are continued.[89] The administration of live vaccines to infants exposed to golimumab in utero is not recommended for 6 months. A risk-benefit assessment of the use of golimumab during pregnancy should always be done.[65, 68]

TNFi have been shown to be excreted in breast milk, but only at minimal amounts. Therefore, this is unlikely to result in systemic immune-suppression and breastfeeding may occur while on this therapy.[93]

In children, golimumab has shown consistent safety profile across weight, concomitant medications and age, similar to adult results and the other TNFi pediatric studies.[94]

Golimumab should not be used in patients with New York Heart Association (NYHA) Grade 3 or 4 cardiac failure and only with caution in milder grades.

In the RA, PsA, AS, and UC golimumab phase III studies no significant differences in adverse events, serious adverse events, and serious infections were found in patients age 65 or older when compared with younger patients. However, caution should be taken when treating the elderly, especially regarding infections occurrence.[34]

Conclusions

Golimumab is a TNFi used for the treatment of several immune-mediated chronic inflammatory diseases. It is well tolerated and associated with low levels of immunogenicity.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

1. Pelechas E, Voulgari PV, Drosos AA. Golimumab for rheumatoid arthritis. J Clin Med. 2019 Mar 20;8(3):387. doi:10.3390/jcm8030387.
2. Shealy DJ, Cai A, Staquet K, Baker A, Lacy ER, Johns L, Vafa O, Gunn G, Tam S, Sague S, et al. Characterization of golimumab, a human monoclonal antibody specific for human tumor necrosis factor α. mAbs. 2010 Aug;2(4):428–39. doi:10.4161/mabs.12304.
3. Wong M, Ziring D, Korin Y, Desai S, Kim S, Lin J, Gjertson D, Braun J, Reed E, Singh RR, et al. TNFalpha blockade in human diseases: mechanisms and future directions. Clin Immunol Orlando Fla. 2008 Feb;126(2):121–36. doi:10.1016/j.clim.2007.08.013.
4. Mantravadi S, Ogdie A, Kraft WK. Tumor necrosis factor inhibitors in psoriatic arthritis. Expert Rev Clin Pharmacol. 2017 Aug;10(8):899–910. doi:10.1080/17512433.2017.1329009.
5. Mitoma H, Horiuchi T, Tsukamoto H, Ueda N. Molecular mechanisms of action of anti-TNF-α agents - Comparison among therapeutic TNF-α antagonists. Cytokine. 2018;101:56–63. doi:10.1016/j.cyto.2016.08.014.
6. Olesen CM, Coskun M, Peyrin-Biroulet L, Nielsen OH. Mechanisms behind efficacy of tumor necrosis factor inhibitors in inflammatory bowel diseases. Pharmacol Ther. 2016 Mar;159:110–19. doi:10.1016/j.pharmthera.2016.01.001.
7. Steeland S, Libert C, Vandenbroucke RE, New A. Venue of TNF targeting. Int J Mol Sci. 2018 May 11;19(5):1–55.
8. Nguyen DX, Ehrenstein MR. Anti-TNF drives regulatory T cell expansion by paradoxically promoting membrane TNF–TNF-RII binding in rheumatoid arthritis. J Exp Med. 2016 Jun 27;213(7):1241–53. doi:10.1084/jem.20151255.
9. Flamant M, Paul S, Roblin X. Golimumab for the treatment of ulcerative colitis. Expert Opin Biol Ther. 2017 Jul 3;17(7):879–86. doi:10.1080/14712598.2017.1327576.
10. Nestorov I. Clinical pharmacokinetics of TNF antagonists: how do they differ? Semin Arthritis Rheum. 2005 Apr;34(5 Suppl1):12–18. doi:10.1016/j.semarthrit.2005.01.004.
11. Baddley JW, Cantini F, Goletti D, Gómez-Reino JJ, Mylonakis E, San-Juan R, Fernandez-Ruiz M, Torre-Cisneros J. ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents). Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2018Jun;24(Suppl 2): S10–20.
12. Chu CQ, Field M, Feldmann M, Maini RN. Localization of tumor necrosis factor alpha in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. Arthritis Rheum. 1991 Sep;34(9):1125–32. doi:10.1002/art.1780340908.
13. Cornillie F, Shealy D, D'Haens G, Geboes K, Van Assche G, Ceuppens J, Wagner C, Schaible T, Plevy SE, Targan SR, et al. Infliximab induces potent anti-inflammatory and local immunomodulatory activity but no systemic immune suppression in patients with Crohn's disease. Aliment Pharmacol Ther. 2001 Apr;15(4):463–73. doi:10.1046/j.1365-2036.2001.00956.x.
14. Bonifati C, Ameglio F. Cytokines in psoriasis. Int J Dermatol. 1999 Apr;38(4):241–51. doi:10.1046/j.1365-4362.1999.00622.x.
15. Knight DM, Trinh H, Le J, Siegel S, Shealy D, McDonough M, Scallon B, Moore MA, Vilcek J, Daddona P, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol. 1993 Nov 1;30(16):1443–53. doi:10.1016/0161-5890(93)90106-L.
16. Hutas G. Golimumab, a fully human monoclonal antibody against TNFalpha. Curr Opin Mol Ther. 2008 Aug;10(4):393–406.
17. Hassett B, Singh E, Mahgoub E, O'Brien J, Vicik SM, Fitzpatrick B. Manufacturing history of etanercept (Enbrel®): consistency of product quality through major process revisions. mAbs. 2017 Nov 29;10(1):159–65. doi:10.1080/19420862.2017.1388483.
18. Lee JU, Shin W, Son JY, Yoo K-Y, Heo Y-S. Molecular basis for the neutralization of tumor necrosis factor α by certolizumab pegol in the treatment of inflammatory autoimmune diseases. Int J Mol Sci. 2017 Jan 23;18(1). [Internet]. [cited 2020 Sep 5]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297857/
19. Thomas SS, Borazan N, Barroso N, Duan L, Taroumian S, Kretzmann B, Bardales R, Elashoff D, Vangala S, Furst DE, et al. Comparative immunogenicity of TNF inhibitors: impact on clinical efficacy and tolerability in the management of autoimmune diseases. a systematic review and meta-analysis. BioDrugs. 2015 Aug 1;29(4):241–58. doi:10.1007/s40259-015-0134-5.
20. Fishwild DM, O'Donnell SL, Bengoechea T, Hudson DV, Harding F, Bernhard SL, Jones D, Kay RM, Higgins KM, Schramm SR, et al. High-avidity human IgG kappa monoclonal antibodies from a novel strain of minilocus transgenic mice. Nat Biotechnol. 1996 Jul;14(7):845–51. doi:10.1038/nbt0796-845.
21. Boyce EG, Halilovic J, Stan-Ugbene O. Golimumab: review of the efficacy and tolerability of a recently approved tumor necrosis factor-α inhibitor. Clin Ther. 2010 Sep;32(10):1681–703. doi:10.1016/j.clinthera.2010.09.003.
22. Gelfer G, Perry L, Deodhar A. Golimumab for the treatment of axial spondyloarthritis. Expert Rev Clin Immunol. 2016;12(1):9–18. doi:10.1586/1744666X.2016.1106941.
23. Martin PL, Cornacoff J, Prabhakar U, Lohr T, Treacy G, Sutherland JE, Hersey S, Martin E. Reviews preclinical safety and immune-modulating effects of therapeutic monoclonal antibodies to interleukin-6 and tumor necrosis factor-alpha in cynomolgus macaques. J Immunotoxicol. 2005 Jul 1;1(3):131–39. doi:10.1080/15476910490894904.
24. Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. Nat Rev Drug Discov. 2010 Oct;9(10):767–74. doi:10.1038/nrd3229.
25. Huffstutter JE, Kafka S, Brent LH, Matucci-Cerinic M, Tang KL, Chevrier M, Sprabery T, DeHoratius RJ. Clinical response to golimumab in rheumatoid arthritis patients who were receiving etanercept or adalimumab: results of a multicenter active treatment study. Curr Med Res Opin. 2017;33(4):657–66. doi:10.1080/03007995.2016.1277195.
26. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M, Park W, Pons-Estel BA, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009Aug;60(8): 2272–83.
27. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae S-C, Palmer W, Zrubek J, et al. Golimumab, a human antibody to tumour necrosis factor given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun 1;68(6):789–96. doi:10.1136/ard.2008.099010.
28. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, Gaylis N, Murphy FT, Neal JS, Zhou Y, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet Lond Engl. 2009 Jul 18;374(9685):210–21. doi:10.1016/S0140-6736(09)60506-7.
29. Inman RD, Davis JC, van der Heijde D, Diekman L, Sieper J, Kim SI, Mack M, Han J, Visvanathan S, Xu Z, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results

of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008 Nov;58(11):3402–12. doi:10.1002/art.23969.
30. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976–86. doi:10.1002/art.24403.
31. Kay J, Fleischmann R, Keystone E, Hsia EC, Hsu B, Mack M, Goldstein N, Braun J, Kavanaugh A. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Ann Rheum Dis. 2015 Mar 1;74(3):538–46. doi:10.1136/annrheumdis-2013-204195.
32. Sandborn WJ, Feagan BG, Marano C. Achieving clinical response and remission in moderate-to-severe ulcerative colitis with golimumab. Gastroenterol Hepatol. 2014Jul;10(7): 452–54.
33. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel J, Reinisch W, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014 Jan 1;146(1):96–109.e1. doi:10.1053/j.gastro.2013.06.010.
34. Simponi [Internet]. European medicines agency. 2018 [cited 2020 Jul 13]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/simponi
35. Zhou H, Jang H, Fleischmann RM, Bouman-Thio E, Xu Z, Marini JC, Pendley C, Jiao Q, Shankar G, Marciniak SJ, et al. Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. J Clin Pharmacol. 2007 Mar;47(3):383–96. doi:10.1177/0091270006298188.
36. Xu Z, Wang Q, Zhuang Y, Frederick B, Yan H, Bouman-Thio E, Marini JC, Keen M, Snead D, Davis HM, et al. Subcutaneous bioavailability of golimumab at 3 different injection sites in healthy subjects. J Clin Pharmacol. 2010 Mar;50(3):276–84. doi:10.1177/0091270009340782.
37. Clinical efficacy and safety: clinical pharmacology pharmacokinetics [Internet]. European Medicines Agency. 2018 [cited 2020 Jun 10]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-clinical-pharmacology-pharmacokinetics
38. Simsek I, Yazici Y. Safety and clinical efficacy of golimumab in the treatment of arthritides. Drug Healthc Patient Saf. 2010;2:169–80.
39. Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T, Lula S, Hawes C, Kola B, Marshall L. et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. BioDrugs Clin Immunother Biopharm Gene Ther. 2017Aug;31(4): 299–316.
40. Leu JH, Adedokun OJ, Gargano C, Hsia EC, Xu Z, Shankar G. Immunogenicity of golimumab and its clinical relevance in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Rheumatol Oxf Engl. 2019 01;58(3):441–46. doi:10.1093/rheumatology/key309.
41. Adedokun OJ, Gunn GR, Leu JH, Gargano C, Xu Z, Sandborn WJ, Rutgeerts P, Shankar G. Immunogenicity of golimumab and its clinical relevance in patients with ulcerative colitis. Inflamm Bowel Dis. 2019 20;25(9):1532–40. doi:10.1093/ibd/izz003.
42. Kavanaugh A, Husni ME, Harrison DD, Kim L, Lo KH, Leu JH, Hsia EC. Safety and efficacy of intravenous golimumab in patients with active psoriatic arthritis: results through week twenty-four of the GO-VIBRANT study. Arthritis Rheumatol Hoboken NJ. 2017;69(11):2151–61. doi:10.1002/art.40226.
43. Rutgeerts P, Feagan BG, Marano CW, Padgett L, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Zhang H, Colombel J-F, et al. Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. Aliment Pharmacol Ther. 2015 Sep;42(5):504–14. doi:10.1111/apt.13291.
44. Sieper J, van der Heijde D, Dougados M, Maksymowych WP, Scott BB, Boice JA, Berd Y, Bergman G, Curtis S, Tzontcheva A, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol Hoboken Nj. 2015 Oct;67(10):2702–12. doi:10.1002/art.39257.
45. Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Chasnyk VG, Panaviene V, Abud-Mendoza C, Reiff A, Alexeeva E, Rubio-Pérez N, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis. 2018 Jan;77(1):21–29. doi:10.1136/annrheumdis-2016-210456.
46. Dehoratius RJ, Brent LH, Curtis JR, Ellis LA, Tang KL. Satisfaction with subcutaneous golimumab and its auto-injector among rheumatoid arthritis patients with inadequate response to adalimumab or etanercept. Patient - Patient-Centered Outcomes Res. 2018 Jun;11(3):361–69.
47. Kavanaugh A, van der Heijde D, McInnes IB, Mease P, Krueger GG, Gladman DD, Gómez-Reino J, Papp K, Baratelle A, Xu W, et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. Arthritis Rheum. 2012 Aug;64(8):2504–17. doi:10.1002/art.34436.
48. Kavanaugh A, McInnes IB, Mease P, Krueger GG, Gladman D, van der Heijde D, Zhou Y, Lu J, Leu JH, Goldstein N, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Ann Rheum Dis. 2014 Sep;73(9):1689–94. doi:10.1136/annrheumdis-2013-204902.
49. Vieira-Sousa E, Alves P, Rodrigues AM, Teixeira F, Tavares-Costa J, Bernardo A, Pimenta S, Pimentel-Santos FM, Gomes JL, Aguiar R, et al. GO-DACT: a phase 3b randomised, double-blind, placebo-controlled trial of GOlimumab plus methotrexate (MTX) versus placebo plus MTX in improving DACTylitis in MTX-naive patients with psoriatic arthritis. Ann Rheum Dis. 2020 Apr 1;79(4):490–98. doi:10.1136/annrheumdis-2019-216500.
50. Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MMS, Tanjong Ghogomu E, Jandu MB, Tugwell P, Wells GA. TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev. 2015 Apr 18;(4):CD005468.
51. Mok CC, Li OC, Chan KL, Ho LY, Hui PK. Effect of golimumab and pamidronate on clinical efficacy and MRI inflammation in axial spondyloarthritis: a 48-week open randomized trial. Scand J Rheumatol. 2015;44(6):480–86. doi:10.3109/03009742.2015.1038300.
52. Sepriano A, Regel A, van der Heijde D, Braun J, Baraliakos X, Landewé R, Van den Bosch F, Falzon L, Ramiro S. Efficacy and safety of biological and targeted-synthetic DMARDs: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. RMD Open. 2017;3(1):e000396.
53. Dragoni G, Le Grazie M, Orlandini B, Rogai F. Golimumab in inflammatory bowel diseases: present and future scenarios. Clin J Gastroenterol. 2019 Feb;12(1):1–9. doi:10.1007/s12328-018-0906-9.
54. Hibi T, Imai Y, Senoo A, Ohta K, Ukyo Y. Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). J Gastroenterol. 2017;52(10):1101–11. doi:10.1007/s00535-017-1326-1.
55. Detrez I, Dreesen E, Van Stappen T, de Vries A, Brouwers E, Van Assche G, Vermeire S, Ferrante M, Gils A. Variability in golimumab exposure: a 'real-life' observational study in active ulcerative colitis. J Crohns Colitis. 2016 May;10(5):575–81. doi:10.1093/ecco-jcc/jjv241.
56. Castro-Laria L, Argüelles-Arias F, García-Sánchez V, Benítez JM, Fernández-Pérez R, Trapero-Fernández AM, Gallardo-Sanchez F, Pallares-Manrique H, Gomez-Garcia M, Cabello-Tapia Mj, Talavera-Fabuel A. et al. Initial experience with golimumab in clinical practice for ulcerative colitis. Rev Espanola Enfermedades Dig Organo Of Soc Espanola Patol Dig. 2016Mar;108(3): 129–32.

57. Bosca-Watts MM, Cortes X, Iborra M, Huguet JM, Sempere L, Garcia G, Gil R, Garcia M, Muñoz M, Almela P, et al. Short-term effectiveness of golimumab for ulcerative colitis: observational multicenter study. World J Gastroenterol. 2016 Dec 21;22 (47):10432–39. doi:10.3748/wjg.v22.i47.10432.
58. Tursi A, Allegretta L, Buccianti N, Della Valle N, Elisei W, Forti G, Faggiani R, Gallina S, Hadad Y, Larussa T, et al. Effectiveness and safety of golimumab in treating outpatient ulcerative colitis: a real-life prospective, multicentre, observational study in primary inflammatory bowel diseases centers. J Gastrointest Liver Dis JGLD. 2017 Sep;26(3):239–44. doi:10.15403/jgld.2014.1121.263.trs.
59. Taxonera C, Rodríguez C, Bertoletti F, Menchén L, Arribas J, Sierra M, Arias L, Martinez-Montiel P, Juan A, Iglesias E, Algaba A. Clinical outcomes of golimumab as first, second or third anti-tnf agent in patients with moderate-to-severe ulcerative colitis. Inflamm Bowel Dis. 2017;23(8):1394–402.
60. Palazzi C, D'angelo S, Gilio M, Leccese P, Padula A, Olivieri I. Golimumab for the treatment of axial spondyloarthritis. Expert Opin Biol Ther. 2017;17(1):129–33. doi:10.1080/14712598.2017.1256387.
61. Russi L, Scharl M, Rogler G, Biedermann L. The efficacy and safety of golimumab as third- or fourth-line anti-tnf therapy in patients with refractory crohn's disease: a case series. Inflamm Intest Dis. 2017 Nov;2(2):131–38. doi:10.1159/000481400.
62. Greener T, Boland K, Steinhart AH, Silverberg MS. The unfinished symphony: golimumab therapy for anti-tumour necrosis factor refractory Crohn's Disease. J Crohns Colitis. 2018 Mar 28;12 (4):458–64. doi:10.1093/ecco-jcc/jjx176.
63. Efficacy and safety of golimumab in Crohn's disease: a French national retrospective study. Abstract - Europe PMC [Internet]. [cited 2020 Jun 20]. Available from: https://europepmc.org/article/med/29027693
64. Palmou-Fontana N, Calvo-Río V, Martín-Varillas JL, Fernández-Díaz C, Mesquida M, Adán A, Hernandez MV, Cordero-Coma M, Alonso OM, Diaz-Valle D, Fernandez-Cid C. Golimumab in refractory uveitis associated to juvenile idiopathic arthritis: multicentre study of 7 cases and literature review. Clin Exp Rheumatol. 2018Aug;36(4): 652–57.
65. Tosi GM, Sota J, Vitale A, Rigante D, Emmi G, Lopalco G, Guerriero S, Orlando I, Iannone F, Frediani B, et al. Efficacy and safety of certolizumab pegol and golimumab in the treatment of non-infectious uveitis. Clin Exp Rheumatol. 2019Aug;37(4): 680–83.
66. Singh J, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. J Rheumatol. 2010 Jun 1;37 (6):1096–104. doi:10.3899/jrheum.091466.
67. Hussar DA. New drugs: golimumab, besifloxacin hydrochloride, and artemether/lumefantrine. J Am Pharm Assoc JAPhA. 2009 Aug;49(4):570–74. doi:10.1331/JAPhA.2009.09523.
68. Kay J, Fleischmann R, Keystone E, Hsia EC, Hsu B, Zhou Y, Goldstein N, Braun J. Five-year safety data from 5 clinical trials of subcutaneous golimumab in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol. 2016 Dec 1;43(12):2120–30.
69. Kim E-M, Uhm W-S, Bae S-C, Yoo D-H, Kim T-H. Incidence of tuberculosis among korean patients with ankylosing spondylitis who are taking tumor necrosis factor blockers. J Rheumatol. 2011 Oct;38(10):2218–23. doi:10.3899/jrheum.110373.
70. Wallis D, Thavaneswaran A, Haroon N, Ayearst R, Inman RD. Tumour necrosis factor inhibitor therapy and infection risk in axial spondyloarthritis: results from a longitudinal observational cohort. Rheumatol Oxf Engl. 2015 Jan;54(1):152–56. doi:10.1093/rheumatology/keu255.
71. Mohan VP, Scanga CA, Yu K, Scott HM, Tanaka KE, Tsang E, Tsai MC, Flynn JL, Chan J. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. Infect Immun. 2001 Mar;69 (3):1847–55. doi:10.1128/IAI.69.3.1847-1855.2001.
72. Godfrey MS, Friedman LN. Tuberculosis and Biologic Therapies: anti-Tumor Necrosis Factor-α and Beyond. Clin Chest Med. 2019;40(4):721–39. doi:10.1016/j.ccm.2019.07.003.
73. Ai J-W, Zhang S, Ruan Q-L, Yu Y-Q, Zhang B-Y, Liu Q-H, Zhang W-H. The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor-α antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. J Rheumatol. 2015 Dec;42 (12):2229–37. doi:10.3899/jrheum.150057.
74. Fonseca JE, Lucas H, Canhão H, Duarte R, Santos MJ, Villar M, Faustino A, Raymundo E. Recommendations for the diagnosis and treatment of latent and active tuberculosis in inflammatory joint diseases candidates for therapy with tumor necrosis factor alpha inhibitors: march 2008 update. Acta Reumatol Port. 2008Mar;33 (1): 77–85.
75. Pham T, Bachelez H, Berthelot J-M, Blacher J, Bouhnik Y, Claudepierre P, Constantin A, Fautrel B, Gaudin P, Goëb V, et al. TNF alpha antagonist therapy and safety monitoring. Joint Bone Spine. 2011 May;78(Suppl 1):15–185. doi:10.1016/S1297-319X(11)70001-X.
76. Segaert S, Hermans C. Clinical signs, pathophysiology and management of cutaneous side effects of anti-tumor necrosis factor agents. Am J Clin Dermatol. 2017 Dec;18(6):771–87. doi:10.1007/s40257-017-0296-7.
77. LE Blay P, Mouterde G, Barnetche T, Morel J, Combe B. Short-term risk of total malignancy and nonmelanoma skin cancers with certolizumab and golimumab in patients with rheumatoid arthritis: metaanalysis of randomized controlled trials. J Rheumatol. 2012 Apr;39(4):712–15. doi:10.3899/jrheum.110982.
78. Michaud TL, Rho YH, Shamliyan T, Kuntz KM, Choi HK. The comparative safety of tumor necrosis factor inhibitors in rheumatoid arthritis: a meta-analysis update of 44 trials. Am J Med. 2014 Dec;127(12):1208–32.
79. Moulis G, Sommet A, Béné J, Montastruc F, Sailler L, Montastruc J-L, Lapeyre-Mestre M. Cancer risk of anti-TNF-α at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. PloS One. 2012;7 (11):e48991. doi:10.1371/journal.pone.0048991.
80. Lemaitre M, Kirchgesner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA. 2017 Nov 7;318(17):1679–86. doi:10.1001/jama.2017.16071.
81. Osterman MT, Sandborn WJ, Colombel J-F, Robinson AM, Lau W, Huang B, Pollack PF, Thakkar RB, Lewis JD. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for crohn's disease. Gastroenterology. 2014 Apr 1;146(4):941–949.e2.
82. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Langholff W, Londhe A, Sandborn WJ. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ Registry. Am J Gastroenterol. 2014 Feb;109(2):212–23. doi:10.1038/ajg.2013.441.
83. Sandborn WJ. State-of-the-art: immunosuppression and biologic therapy. Dig Dis Basel Switz. 2010;28(3):536–42. doi:10.1159/000320413.
84. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr 15;362(15):1383–95. doi:10.1056/NEJMoa0904492.
85. Dulai PS, Siegel CA. The risk of malignancy associated with the use of biological agents in patients with inflammatory bowel disease. Gastroenterol Clin North Am. 2014 Sep;43(3):525–41. doi:10.1016/j.gtc.2014.05.010.
86. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275–85.
87. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab,

etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf. 2011 Feb;20(2):119–30. doi:10.1002/pds.2046.
88. Zidi I, Bouaziz A, Mnif W, Bartegi A, Ben Amor N. Golimumab and malignancies: true or false association? Med Oncol Northwood Lond Engl. 2011 Jun;28(2):641–48. doi:10.1007/s12032-010-9490-7.
89. Hassid B, Mahadevan U. The use of biologic therapy in pregnancy: a gastroenterologist's perspective. Curr Opin Rheumatol. 2014 May;26(3):347–53. doi:10.1097/BOR.0000000000000048.
90. Bröms G, Granath F, Ekbom A, Hellgren K, Pedersen L, Sørensen HT, Stephansson O, Kieler H. Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor agents during pregnancy. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2016Feb;14(2): 234–241.e1–5.
91. Weber-Schoendorfer C, Oppermann M, Wacker E, Bernard N, Beghin D, Cuppers-Maarschalkerweerd B, Richardson JL, Rothuizen LE, Pistelli A, Malm H, et al. network of French pharmacovigilance centres, Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: a prospective multicentre cohort study. Br J Clin Pharmacol. 2015 Oct;80(4):727–39. doi:10.1111/bcp.12642.
92. Johansen CB, Jimenez-Solem E, Haerskjold A, Sand FL, Thomsen SF. The use and safety of TNF inhibitors during pregnancy in women with psoriasis: a review. Int J Mol Sci. 2018 May 3;19(5):1349. [Internet]. [cited 2020 Jul 12]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5983707/
93. Ben-Horin S, Yavzori M, Kopylov U, Picard O, Fudim E, Eliakim R, Chowers Y, Lang A. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis. 2011 Dec;5(6):555–58. doi:10.1016/j.crohns.2011.05.006.
94. Hyams JS, Chan D, Adedokun OJ, Padgett L, Turner D, Griffiths A, Veereman G, Heyman MB, Rosh JR, Wahbeh G, et al. Subcutaneous Golimumab in Pediatric Ulcerative Colitis: pharmacokinetics and Clinical Benefit. Inflamm Bowel Dis. 2017;23 (12):2227–37. doi:10.1097/MIB.0000000000001262.