Clinical Efficacy and Adverse Effects of Golimumab in the Treatment of Rheumatoid Arthritis

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ABSTRACT: Golimumab is a fully human monoclonal antibody targeting tumor necrosis factor-alpha (TNFα), an important cytokine in the pathogenesis of rheumatoid arthritis (RA) and other arthritides. Golimumab was approved for the treatment of rheumatoid arthritis with methotrexate (MTX) and with or without MTX for psoriatic arthritis and ankylosing spondylitis. Administration is by monthly subcutaneous injection. In this review we present some of the major clinical trials evaluating the efficacy of golimumab with or without concomitant MTX in RA patients, including patients resistant to previous biologic treatments. In addition, we collected data on safety and adverse effects encountered in clinical trials. Current data show golimumab to be an effective and safe choice for the treatment of various inflammatory arthritides.

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KEY WORDS: tumor necrosis factor (TNF), golimumab, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA)

Rheumatoid arthritis is an autoimmune disease manifesting primarily as an inflammatory arthritis. It is associated with chronic inflammation of synovial joints, mostly hands and feet, as well as systemic extraarticular inflammation. The disease is progressive, and over time patients develop joint destruction and bone erosion that eventually leads to personal and vocational disability [1-3]. The impact on individual patients and on society is high, since impaired health can be life-long and significantly reduces both quality of life and function [3-5]. The pathophysiology of the disease involves the overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukins-1 and 6 [6,7].

TNFα plays a key role in driving inflammation not only in RA but also in other immune-mediated diseases such as ankylosing spondylitis, psoriatic arthritis and inflammatory bowel diseases [6-9]. It elicits the production of other pro-inflammatory cytokines and adhesion molecules, increases endothelial layer permeability and, consequently, increases leukocyte recruitment into the involved joint. TNFα upregulates osteoclasts and metalloproteinases, inducing bone erosion [7,10]. In the past decade, numerous drugs targeting TNFα have been developed due to this pivotal role in the pathophysiology of many rheumatologic diseases. Infliximab, etanercept and adalimumab have all proven effective in the treatment of RA, dramatically ameliorating clinical manifestations, reducing joint damage and radiographic progression, and inducing remissions [11,12]. TNFα inhibitors are biological agents with significant disease-modifying effects [13].

Other treatment options for rheumatoid arthritis include the older non-disease-modifying antirheumatic drugs, such as prednisolone and non-steroidal anti-inflammatory drugs and the widely used non-biological DMARD methotrexate. However, their potential toxicity and suboptimal efficacy prompted the development of additional treatment options. Aside from the anti-TNFα drugs already mentioned, other newly available biological agents target the IL-1 receptor (anakinra), the co-stimulatory molecule, CD28 (abatacept), the IL-6 receptor (tocalizumab) and B cells (rituximab).

Anti-TNFα drugs include two subtypes, antibodies to TNFα and fusion proteins consisting of a TNFα receptor coupled with the Fc domain of human immunoglobulin G1, Etanercept (Enbrel®, Immunex Pfizer, USA). Infliximab (Remicade®, Janssen Biotech, USA) is a chimeric monoclonal anti-TNFα antibody. Adalimumab (Humira®) Abott Laboratories, USA), Certolizumab pegol (Cimzia®, UCB, USA) and golimumab (Simponi® Janssen Biotech, USA) are fully human anti-TNFα monoclonal antibodies [Table 1] [7-9,14,15].

WHAT IS GOLIMUMAB?

Golimumab is a TNFα inhibitor that binds to the specific receptors of both transmembrane and soluble TNFα and blocks their action. Golimumab was approved in April 2009 by the U.S. Food and Drug Administration for the treatment of moderate to severe RA with MTX, and for use with or without

TNFα = tumor necrosis factor-alpha
RA = rheumatoid arthritis
DMARD = disease-modifying antirheumatic drugs
IL = interleukin
MTX = methotrexate

Table 1. FDA approved anti-TNFα for the treatment of rheumatoid arthritis

Name	Infliximab	Etanercept	Adalimumab	Certolizumab pegol	Golimumab
Trade name	Remicade®	Enbrel®	Humira®	Gimzia®	Simponi®
Description	A human-mouse chimeric monoclonal antibody	A fusion protein of two TNFα receptor extracellular domains and a Fc portion of human IgG	Fully human monoclonal antibody (IgG1) to TNFα	Human polyethyleneglycolated Fab fragment to TNFα	Fully human monoclonal antibody (IgG1) to TNFα
Route	Intravenously	Subcutaneously	Subcutaneously	Subcutaneously	Subcutaneously
Frequency	Every 8 weeks	Once or twice a week	Every 2 weeks	Every 2 weeks	Every 4 weeks
Approved dosage	100 mg	25 mg	40 mg	200 mg	50 mg
Approval time for RA treatment by the FDA	August 1998	November 1998	December 2002	May 2009	April 2009

FDA = Food & Drug Administration, Ig = immunogobulin

MTX in PsA and AS [16]. In adults it is administered by subcutaneous injection as a monthly dose of 50 mg, a less frequent dosing regimen than the other anti-TNFα drugs currently in use. Maximum serum concentrations are reached within 2–6 days. The median terminal half-life is approximately 2 weeks. Steady state is achieved by 12 weeks [17] .

EFFICACY IN RA

Clinical response can be evaluated by using the American College of Rheumatology response criteria for RA. ACR50 response is defined as 50% improvement in both tender and swollen joint counts and 50% improvement in three of the following five variables: patient global assessment, physician global assessment, pain scores, Health Assessment Questionnaire score and acute-phase reactants such as erythrocyte sedimentation rate or C-reactive protein [18]. The Disease Activity Score is a composite parameter calculated on the basis of evaluation of 28 tender and swollen joints, the levels of either ESR or CRP and the result of the visual analogue scale reflecting the patient's general health (in mm ranging from 0 to 100) [19].

Golimumab is a new TNFα inhibitor, which binds to the specific receptors of both transmembrane and soluble TNFα and blocks their action

Clinical trials have assessed the efficacy of golimumab in patients with active RA in reducing symptoms and signs upon administration with or without concomitant MTX. Emery and co-authors [20] evaluated the safety and efficacy of golimumab in patients naïve to either MTX or anti-TNF (n=637) with active RA during a 24 week follow-up. Combining golimumab 50 mg with MTX (but not golimumab 100 mg with placebo) was found to be superior, achieving an ACR50 response at 24 weeks, to MTX with placebo (40.5% vs. 29.4%, respectively, $P = 0.038$). As observed with all other anti-TNFα agents, monotherapy with golimumab was not superior to monotherapy with MTX. However, the combination of both drugs provided significant synergism manifested by composite parameters such as ACR20, 50 and 70 responses as well as DAS28 scores or swollen joint counts and biological parameters such as hemoglobin and CRP serum concentrations.

Keystone et al. [21] reported that the combination of golimumab and MTX was superior to either golimumab or MTX alone in improving physical functioning and ameliorating signs and symptoms of RA in patients (n=444) who were non-responsive or partially responsive to antecedent MTX therapy. Once again golimumab and placebo was not significantly superior to MTX and placebo in these assessments. At 14 weeks, golimumab 50 mg (55.1%) or 100 mg (56.2%) with MTX was superior to placebo with MTX (33.1%) in achieving ACR20 response ($P < 0.001$). Similar results were seen at 24 weeks and maintained through 52 weeks [22].

Smolen et al. [23] demonstrated that golimumab may be a therapeutic option for patients who were previously treated with other anti-TNF drugs that were discontinued due to ineffectiveness or intolerance. In their study (n=461), switching from another anti-TNF to golimumab (with a concomitant DMARD) was effective and well tolerated. At week

PsA = psoriatic arthritis
AS = ankylosing spondylitis
ACR = American College of Rheumatology
ESR = erythrocyte sedimentation rate
CRP = C-reactive protein

DAS28 = Disease Activity Score

14, golimumab 50 mg (35%) and 100 mg (38%) was superior to placebo (18%) in achieving an ACR20 response ($P < 0.001$) regardless of the reason for discontinuing previous anti-TNF drugs. Similar results were seen in achieving ACR50, 70 and DAS28 responses.

A complementary study by Kay and team [24] in 172 patients showed that golimumab in combination with MTX was effective in reducing signs and symptoms in RA patients who responded inadequately to prior treatment with MTX alone. At week 16, 61.3% of patients in the combined golimumab + MTX groups and 79.4% of patients receiving 100 mg golimumab every 2 weeks reached the ACR20 compared to 37.1% of patients from the MTX+placebo group ($P < 0.001$). Significant improvements were also observed with the combination therapy at week 16 for ACR50, ACR 70 and DAS28.

Golimumab has been approved by the FDA for the treatment of moderate to severe rheumatoid arthritis with methotrexate and for use with or without methotrexate in psoriatic arthritis and ankylosing spondylitis

SAFETY

The most frequently reported adverse events with golimumab use are nausea, upper respiratory tract infection, increased liver enzymes, increased aspartate aminotransferase and alanine aminotransferase levels, dyspepsia and headache [20]. Other adverse events include reactions to subcutaneous administration, most commonly erythema and infections [20-22]. Important adverse effects most extensively related to TNFα blockers are fusion reaction, lymphoma, an increased risk of infections including tuberculosis and fungal infections, congestive heart failure, demyelinating disease, a lupus-like syndrome and induction of autoantibodies [14,25].

Serious adverse effects of golimumab are reported to occur in 2%–7% of patients [Table 2] and non-serious in approximately 60%–80%, similar to the incidence after placebo treatment [26]. In an indirect comparison there are no significant differences between golimumab and other biological agents in rates of adverse effects. Golimumab is less likely to cause serious infections than certolizumab pegol and was found to be associated with significantly fewer withdrawals due to adverse effects than infliximab [25]. No significant relation was found between golimumab dosing and incidence of adverse effects [26]. Overall, data obtained from clinical trials suggest that golimumab is safe and well tolerated. On the other hand, it is important to keep in mind that none of these trials defined safety as their primary endpoint and all were of short duration [26].

The safety profile of golilumab is similar to that of other TNFα inhibitors

Infectious diseases

Bacterial and viral infections, particularly of the respiratory system, cutaneous and soft tissues and the urinary tract, are common in patients receiving anti-TNF therapy [14,27]. Tuberculosis is the most common opportunistic infection due to the role of TNFα in the host defense against *Mycobacterium tuberculosis*, in granuloma formation and suppression of latent disease. All patients should be screened for latent or active tuberculosis prior to treatment with all anti-TNF drugs, including golimumab [14,28,29].

In clinical studies of golimumab, infection is the leading adverse effect (30%). The overall incidence of infection was similar in patients treated with placebo or golimumab. However, upper respiratory tract infections were slightly more common in patients treated with golimumab compared to placebo (12% vs. 7%) [16,26,30]. Serious infections observed in patients treated with golimumab include sepsis, pneumonia, cellulitis, gastroenteritis, otitis media, urinary tract infection, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection [26]. The incidence of these infections was not found to be significantly higher compared to the placebo-treated group (1.4% vs. 1.3%) [30].

Malignancies

More cases of lymphoma have been documented in patients under anti-TNF treatment than in controls. In clinical trials, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% confidence interval 0.03–0.77) in a combined golimumab group compared with an incidence of 0 (95% CI 0.0–0.96) in the placebo group. The incidence of lymphoma was increased 3.8-fold compared to the general population in the United States [30]. However, it should be noted that even without anti-TNF treatment, RA patients are at increased risk for developing hematologic malignancies due to the con-

Table 2. Safety outcomes from open-label extension studies*

	Serious adverse effects, events	Serious infections*, events	TB, events	Lymph cancer, events	Congestive heart failure, events
Rates	16.1% (22)	2.2% (3)	0.0% (0)	0.0% (0)	0.7% (1)
Relative risk	1.03 (0.67–1.58)	1.43 (0.82–2.5)			1.19 (0.7–2.02)

The numbers in parentheses signify the number of patients
*These studies included 137 patients during 3–60 months of follow-up. Based on refs [15,16,26;30]
**Mostly include infections associated with death, hospitalization or treatment with IV antibiotics

CI = confidence interval

tinuous inflammatory process and B cell activation [31]. An increased incidence of malignancies other than lymphoma has not been associated with golimumab [30].

Congestive heart failure.
Golimumab has not been tested in patients specifically diagnosed with congestive heart failure [30]. Other anti-TNF drugs, such as adalimumab, have been shown to rarely worsen CHF and their avoidance is recommended in these patients [32]. Golimumab should be used carefully in CHF patients and discontinued with onset of exacerbation.

Demyelinating disorders
Onset or exacerbation of central nervous system demyelinating disorders has been reported with the use of anti-TNF drugs. However, their incidence has not been found to increase when compared with the general population [14,33-35].

IMMUNOGENICITY

Antibodies to golimumab were detected in 57 patients (4%) treated with golimumab in phase 3 trials through week 24 [30]. Combined treatment with golimumab and MTX showed a lower incidence of antibodies than treatment with golimumab alone (approximately 2% vs. 7%, respectively) [20,30]. Increased incidence of antinuclear antibodies has also been observed during golimumab treatment. Among patients treated only with golimumab, 27% developed ANA compared to 10% receiving placebo [36]. Similarly, ANA are also increased in patients treated with golimumab and MTX compared to placebo (12.2% vs.14.9% respectively) [21].

GOLIMUMAB FOR PSORIATIC ARTHRITIS AND ANKYLOSING SPONDYLITIS

Golimumab was assessed for PsA and AS in two prospective double-blind randomized studies. In the GO-RAISE study, at week 14, 60% of AS patients treated with golimumab (50 mg or 100 mg) achieved a 20% improvement in the Assessment in AS International working Group criteria (ASAS20) compared to 22% of AS patients in the placebo group [37,38]. For PsA, in the GO-REVEAL study 48% of patients treated with golimumab (50 or 100 mg) achieved an ACR20 response as compared to 9% in the placebo group [37,39].

SUMMARY

Golimumab is a human monoclonal antibody to TNFα that has been approved for treatment of RA, AS and PsA at a dose of 50 mg for all indications. Its efficacy and safety have been demonstrated in RA patients naïve or resistant to MTX and in those who responded inadequately to prior treatment with another anti-TNF drug.

In clinical trials golimumab was significantly better than placebo in achieving ACR20/50/70 and lowering DAS28 score at 5–6 months follow-up. It was also found effective for AS and PsA. An obvious advantage is its once-monthly subcutaneous dosing, permitting patient self-administration. Total adverse effects for golimumab appear to be similar to those of other biological agents. However, golimumab was found to be less likely to be withdrawn due to adverse effects than infliximab and less likely to cause serious infections than certolizumab pegol. Long-term studies are necessary to determine the durability of response to golimumab as well as delayed or cummulative adverse effects.

CHF = congestive heart failure
ANA = antinuclear antibodies

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Capsule

Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation

Commensal bacteria that colonize mammalian barrier surfaces are reported to influence T helper type 2 (T_H2) cytokine-dependent inflammation and susceptibility to allergic disease, although the mechanisms that underlie these observations are poorly understood. Hill and colleagues found that deliberate alteration of commensal bacterial populations via oral antibiotic treatment resulted in elevated serum immunoglobulin (Ig) E concentrations, increased steady-state circulating basophil populations and exaggerated basophil-mediated T_H2 cell responses and allergic inflammation. Elevated serum IgE levels correlated with increased circulating basophil populations in mice and subjects with hyperimmunoglobulinemia E syndrome. Furthermore, B cell-intrinsic expression of myeloid differentiation factor 88 (MyD88) was required to limit serum IgE concentrations and circulating basophil populations in mice. Commensal-derived signals were found to influence basophil development by limiting proliferation of bone marrow-resident precursor populations. Collectively, these results identified a previously unrecognized pathway through which commensal-derived signals influence basophil hematopoiesis and susceptibility to T_H2 cytokine-dependent inflammation and allergic disease.

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Eitan Israeli

"The only gift is giving to the poor
All else is exchange"

Thiruvalluvar (c. 30 BCE), Tamil poet and philosopher