

Role of golimumab, a TNF-alpha inhibitor, in the treatment of the psoriatic arthritis

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Abstract: Psoriatic arthritis (PsA) is an inflammatory arthritis that affects many psoriasis patients and can often have a debilitating disease progression. Golimumab is a new tumor necrosis factor (TNF) antagonist recently approved by the FDA for controlling signs and symptoms of psoriatic arthritis. In a Phase III clinical trial in patients with PsA, patients receiving golimumab showed significant improvement in the signs and symptoms of disease. It was usually well tolerated, but adverse events generally occurred more in patients receiving golimumab compared to placebo. Golimumab has also recently shown efficacy in slowing structural damage in PsA. This new biologic therapy provides physicians with another option in the treatment of this inflammatory arthritis while offering patients certain advantages over other TNF antagonists.

Keywords: golimumab, psoriatic arthritis, TNF-alpha inhibitor

Introduction

Psoriatic arthritis is a seronegative inflammatory arthritis that affects approximately 0.25% of the general population in the United States and approximately 14% of psoriasis patients according to one recent study, though reported numbers have reached over 40%.¹⁻³ Psoriatic arthritis can often present a diagnostic challenge due to a wide range of clinical presentations, degrees of severity, and may be difficult to distinguish from other inflammatory arthritides. The disease progression of PsA is variable and patients often present only with skin involvement for years before developing any joint symptoms. The symptoms described by psoriatic arthritics may present as less severe relative to other inflammatory arthritis such as rheumatoid arthritis (RA), and may be deemed a milder form despite underlying structural damage.³ A complicated clinical picture and a paucity of symptoms may cause a delay in diagnosis and treatment which could then lead to a quiet progression of the structural damage.

Once diagnosed, appropriate treatment of PsA, based the severity of disease, should be initiated to improve the signs and symptoms and minimize the negative disease impact on patients' lives. For mild disease, this typically involves the use of nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and/or corticosteroid injections. For moderate to severe disease, more aggressive treatment is necessary in order to inhibit progression of structural damage. Disease-modifying antirheumatic drugs (DMARDs) are available, but their efficacy in PsA when used alone has not been well established. TNF blockade with or without methotrexate has been demonstrated to control signs and symptoms, inhibit X-ray progression and improve quality of life in patients with PsA.⁴⁻⁶

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There are a number of options for biologic treatments, particularly the TNF antagonists. Most show similar efficacy and side effect profiles. Golimumab, one of the newest TNF blockers, was recently shown to be efficacious in improving not only the signs and symptoms of PsA, but also in treating the structural damage caused by the disease making it a reasonable option in treating moderate to severe PsA.

Mode of action

Golimumab is one of the newer TNF antagonists to become available and is currently indicated for controlling the signs and symptoms of active PsA in adult patients. Manufactured by Centocor Ortho Biotech, Inc (Horsham, PA, USA) under the trade name Simponi, golimumab is a fully human anti-TNF IgG monoclonal antibody with affinity for both soluble and transmembrane TNF.⁷ It targets and neutralizes a key contributing factor in the inflammatory process as well as the pathophysiology of chronic inflammatory diseases, including RA, PsA, and ankylosing spondylitis (AS).⁸

Pharmacokinetics

Serum concentrations of golimumab were generally dose-proportional in Phase III clinical trials,^{9,10} though Kay et al also reported a large variation between patients.¹¹ Steady-state concentrations of golimumab were achieved by Week 12 in these trials.⁹⁻¹¹

Xu et al determined population pharmacokinetic parameters of golimumab based on data collected in the GO-REVEAL study of patients with PsA.^{9,12} Analysis of serum concentrations showed an apparent clearance of 1.38 ± 0.04 L/d and an apparent volume of distribution of 24.9 ± 1.04 L for patients weighing a standard 70 kg.¹² The authors found that body weight was a significant covariate for both the apparent clearance and apparent volume of distribution. Patients receiving the 50 mg dose of golimumab and with a body weight greater than 100 kg showed less improvement based on American College of Rheumatology (ACR) criteria than those patients weighing less than 100 kg receiving the same dose. This difference in response rates based on body weight was not as evident in the patients receiving the 100 mg dose of golimumab, and the authors suggested that a dose adjustment may be necessary in patients weighing over 100 kg.¹² Other significant covariates found for the apparent clearance included antibodies to golimumab status, smoking status, and baseline C-reactive protein level. The use of concomitant medications, including NSAIDs, corticosteroids, and methotrexate, was also analyzed for potential effects. In the group receiving the 50 mg golimumab dose,

there appeared to be a reduction in clearance of golimumab with concomitant use of methotrexate, but this effect was not seen in the group receiving the 100 mg dose of golimumab and overall was not significant. The authors also determined a half-life for golimumab of 12.5 days.¹²

Efficacy

In the Phase III clinical trial of golimumab in patients with active PsA, significant improvement in the signs and symptoms of the disease was shown following treatment with golimumab at doses of 50 mg and 100 mg every 4 weeks.⁹ Kavanaugh et al also found that 51% of patients treated with 50 mg golimumab and 45% of patients treated with 100 mg of golimumab achieved an American College of Rheumatology 20% improvement criteria (ACR20) response at week 14, the study's primary endpoint, compared to only 9% in patients receiving placebo ($P < 0.001$ for both comparisons). This efficacy of golimumab was maintained at week 24 of the trial where 52% of patients in the 50 mg golimumab and 61% in the 100 mg golimumab groups achieved an ACR20 response compared to only 12% in the placebo group ($P < 0.001$ for both comparisons).⁹ This response is comparable to that observed with other TNF antagonists (see Table 1).

Approximately half of the patients in this trial were also taking stable doses of concomitant methotrexate. The proportion of patients on methotrexate and their mean dosages were similar in all treatment groups and the ACR20 response at week 14 was observed regardless of methotrexate use.⁹

Patients in this same study with at least 3% body surface area (BSA) affected by psoriasis were also evaluated for changes in the Psoriasis Area and Severity Index (PASI) score. It was found that 40% of these patients in the 50 mg golimumab group and 58% in the 100 mg golimumab group achieved a 75% improvement in their PASI score (PASI75) at week 14 compared to only 3% of patients receiving placebo ($P < 0.001$ for both comparisons). At week 24, 56% of patients in the 50 mg golimumab group and 66%

Table 1 Efficacy comparison of golimumab (50 mg once monthly) and other TNF antagonists^{4-6,9}

TNF antagonist	ACR20 response at week 12 or 14 ^a	PASI75 at week 24
Etanercept	59%	23%
Adalimumab	58%	59%
Infliximab	58%	60%
Golimumab	51%	56%

^aACR20 response observed at week 12 for etanercept and adalimumab, at week 14 for infliximab and golimumab.

in the 100 mg group achieved a PASI75 compared to 1% in the placebo group ($P < 0.001$ for both comparisons) (Table 1).

Changes in nail involvement were also assessed using the Nail Psoriasis Severity Index (NAPSI) and Physician's Global Assessment (PGA) of psoriatic nail disease. Patients treated with golimumab showed significant improvement in nail involvement compared to placebo at week 14 and at week 24.⁹

The proportion of patients with enthesitis in the 50 mg and 100 mg golimumab groups was 49% and 50%, respectively, compared to 69% in the placebo group at week 24 ($P = 0.002$ and $P = 0.003$, respective comparisons). Significant improvement in the PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was also observed. A 60% median change was observed in those receiving 50 mg golimumab and 67% in those receiving 100 mg golimumab compared to only a 12% median score change in those receiving placebo ($P < 0.001$ for both). There was no significant difference observed in the proportion of patients with dactylitis through week 24, though the severity of dactylitis had significantly improved in patients treated with 100 mg of golimumab relative to placebo.⁹

Kavanaugh et al also showed that golimumab was efficacious in improving physical function and quality of life. They observed that patients treated with golimumab had significantly improved Health Assessment Questionnaire (HAQ) and Short-Form 36 (SF-36) scores at week 14 compared to placebo.⁹

Long-term efficacy of golimumab has been observed; with continued response rates through 2 years of treatment.¹³ The proportion of patients who remained on the 50 mg dose of golimumab achieving an ACR20 response at weeks 52 and 104 were 78% and 91%, respectively. Patients who remained on the 100 mg dose also showed continued response at week 52 with 81% achieving an ACR20, though the proportion of patients with that response decreased to 73% at week 104. In the 50 mg group, 62% and 69% of patients achieved a PASI75 at weeks 52 and 104, respectively. In the group treated with 100 mg of golimumab, 70% and 76% of patients achieved a PASI75 at weeks 52 and 104, respectively. Improvement in HAQ scores was also maintained for both groups through week 104.¹³

Radiographic changes

Additionally, golimumab has been shown to slow structural joint damage, specifically articular erosions and joint space narrowing, which has been observed radiographically.

Kavanaugh et al recently reported that PsA patients receiving golimumab showed significantly less progression of joint space disease at week 52 of treatment compared to those receiving placebo.¹⁴

Safety and tolerability

Golimumab was usually well tolerated in Phase III trials, but adverse events generally occurred more in patients receiving golimumab compared to placebo. Kavanaugh et al reported adverse events in 65% of all golimumab-treated patients compared to 59% of those receiving placebo, and serious adverse events in 2% and 6% of patients, respectively.⁹ Similarly, Inman et al reported 85.6% of patients treated with golimumab and 76.6% of patients receiving placebo reported at least one adverse event, whereas 5.4% of the golimumab-treated patients reported at least 1 serious adverse event compared to 6.5% of patients receiving placebo.¹⁰

The side effect profile of golimumab is similar to that of other TNF antagonists.⁴⁻⁶

Common adverse reactions

Injection site reactions were among the common adverse reactions reported in Phase III clinical trials of golimumab.^{9-11,15-17} One trial reported injection site reactions at a rate of 8.7% in the 50 mg golimumab group and 6.4% in the 100 mg group compared to 2.6% in the placebo group.¹⁰ Kavanaugh et al reported that injection site reactions in the combined golimumab group (3%) were comparable to the placebo group (3%).⁹ The most common reaction was erythema, which was generally mild and did not lead to discontinuation of treatment.^{9,11,15-17} No anaphylactic reactions have been reported for golimumab in clinical trials. Other common adverse reactions in these trials included upper respiratory infections, nasopharyngitis, and headache.^{9,11,15,16} Similar common adverse events were observed in clinical trials of other TNF antagonists.⁴⁻⁶

Infections

In Phase III clinical trials, more subjects receiving golimumab developed any type of infection during the study periods compared to those receiving placebo⁹⁻¹¹ or methotrexate alone.¹⁶ Though uncommon, serious infections, including sepsis and pneumonia, have been reported in patients taking golimumab similar to those taking other TNF antagonists. Kay et al reported 3 patients treated with golimumab who developed pneumonia, including 1 patient who also developed septic shock, and 1 patient in the placebo group developed a lower respiratory infection.¹¹ Because

infections can be serious, even fatal,¹⁶ golimumab should not be prescribed to patients with evidence of an active infection or are immunocompromised.

TNF is thought to play an important role in host defense against infection, particularly against intracellular bacteria,⁸ inferring a degree of susceptibility to these types of infections with the use of TNF antagonists. In Phase III trials of golimumab, anti-tuberculosis treatment was initiated prior to entering the study in patients who showed evidence of latent tuberculosis infection.^{9,10,16,17} One case of tuberculosis of the spine was reported in a patient receiving golimumab during these trials.¹⁷ The diagnosis had been made only after the patient's treatment with golimumab began, was based on the observation of caseating granulomas in a surgical specimen, and the diagnosis was not confirmed by any other method. No other cases of active or reactivation tuberculosis were reported in clinical trials. It is recommended that all patients be screened for evidence of latent infection and treated appropriately prior to initiation of treatment with golimumab.

Abnormal laboratory values

Elevations in liver enzymes were reported in trials of golimumab. More patients receiving golimumab had increased liver transaminases compared to placebo. Kavanaugh et al reported 24% of patients in the 50 mg golimumab group, 35% in the 100 mg golimumab group, and 18% in the placebo group had elevations in alanine aminotransferase (ALT) levels. Aspartate aminotransaminase (AST) was also elevated in 18%, 13%, and 10% of patients, respectively.⁹ Patients were generally asymptomatic and most of these elevations were not serious.^{9,10} Many of the patients with increased AST and ALT levels were concurrently receiving other medications such as isoniazid for treatment of latent tuberculosis^{9,10} or methotrexate.¹⁰ However, Emery et al did not find an increased risk of serious AST or ALT elevations with concomitant use of golimumab and isoniazid.¹⁷

Two cases of anemia were reported in a Phase III clinical trial in patients receiving 100 mg of golimumab plus placebo.¹⁷

Malignancy

Patients treated with any of TNF antagonists, including golimumab, may be at higher risk for developing certain malignancies, including lymphoma, than the general population. It is not clear, however, if the presence of a chronic inflammatory disease, like rheumatoid arthritis, itself may predispose patients to developing lymphoma.¹⁸ Only solid malignancies were reported in one Phase III clinical trial,

two cases of basal cell carcinoma and one case of prostate cancer in the group receiving a higher dose of golimumab (100 mg monthly) compared to no reports of malignancy in the lower golimumab dose (50 mg monthly) or placebo groups through week 24 of the study.⁹ Smolen et al reported a case of squamous cell carcinoma of the skin in a patient receiving 50 mg golimumab, lymphoma in a patient receiving 100 mg golimumab, and pancreatic cancer in a patient receiving placebo.¹⁵ Emery et al reported breast cancer and squamous cell carcinoma of the lip in patients receiving methotrexate plus placebo, another case of breast cancer in a patient receiving 50 mg golimumab plus methotrexate, and Hodgkin's lymphoma in a patient receiving 100 mg golimumab plus methotrexate.¹⁷ Keystone et al also reported four malignancies, two cases of non-melanoma skin cancer in patients receiving 100 mg golimumab alone and one case of breast cancer in a patient receiving 100 mg golimumab and methotrexate compared to 1 case of basal cell cancer in a patient taking methotrexate alone.¹⁶

Congestive heart failure

TNF antagonists, including golimumab, can potentially exacerbate CHF.¹⁹ In a Phase III clinical trial in patients with rheumatoid arthritis despite methotrexate treatment one patient reported congestive heart failure.¹¹ New onset CHF has also been reported with other TNF antagonists. Care should be taken when prescribing golimumab in patients with CHF and they should be monitored routinely for signs and symptoms of deterioration of their condition or newly developing CHF.

Autoimmunity

The development of autoantibodies, particularly antinuclear and anti-dsDNA antibodies, is associated with the use of TNF antagonists.²⁰ Inman et al reported 10.1% of patients receiving 50 mg golimumab, 14.8% of those receiving 100 mg golimumab, and 12.9% receiving placebo were newly positive for antinuclear antibodies, but only one of these patients developed anti-dsDNA antibodies.¹⁰ In another clinical trial, the rate of antinuclear antibodies in the golimumab plus methotrexate treated groups was 12.2% (combined) and was comparable to placebo plus methotrexate (14.9%). The rate of antinuclear antibodies was found to be higher in the golimumab alone group (29.3%).¹⁶ One case of systemic lupus erythematosus (SLE) was reported in Phase III clinical trials. The patient had tested positive for antinuclear antibodies prior to treatment initiation and developed SLE within days after receiving their first dose of golimumab.¹⁵ Currently, there

are no recommendations for monitoring of autoantibodies in patients taking TNF antagonists. Antibodies to golimumab itself were found in 2.1% to 6.3% of golimumab-treated patients^{9,16,17} in Phase III clinical trials, though none of the patients receiving methotrexate at baseline developed antibodies to the drug.⁹

Warnings

Potential class effects

Other TNF antagonists have been associated with additional adverse events that were not reported for golimumab in the above referenced Phase III clinical trials. Because of the potential for class effects, it is important to consider these additional risks when prescribing golimumab to patients. There are reports of new onset and exacerbation of the demyelinating disorders, including multiple sclerosis, in patients while taking TNF antagonists.^{21,22}

Reactivation of hepatitis B virus has occurred in chronic carriers taking TNF antagonists and was even fatal in some cases, although most of these patients were also taking other immunosuppressive drugs.⁷ Chronic hepatitis C infection is not a contraindication to the use of TNF antagonists, but these patients should be closely monitored during treatment.²³

There are also reports of other hematologic cytopenias in patients receiving other TNF antagonists, though often in combination with drugs that can suppress bone marrow function. The use of TNF antagonists may also exacerbate psoriasis in patients or cause new onset psoriasis.

Interactions

The manufacturer also recommends that golimumab not be prescribed if the patient is taking abatacept or anakinra, due to the increased risk of serious infections with concurrent use.⁷

Use of golimumab in practice

This new biologic therapy provides physicians with another option in the treatment of these often debilitating diseases and may offer certain advantages over other biologic therapies. Smolen et al showed that golimumab was effective at improving the signs and symptoms of active rheumatoid arthritis in patients who had previously discontinued other TNF antagonists mainly for lack of effectiveness, intolerance, or inaccessibility. The authors suggest that golimumab is a possible alternative therapy when other TNF antagonists are not tolerated.¹⁵

Another advantage of golimumab over other TNF antagonists is that its dosing schedule may offer more convenience to the patient. It is dosed once monthly as a subcutaneous

injection that can be self-administered at home.⁷ This schedule is compared to that of other TNF blockers, including intravenous infusions of infliximab every 4 to 8 weeks, weekly subcutaneous dosing of etanercept, and every other week subcutaneous dosing of adalimumab for treatment of the same indications.^{24–26}

Conclusion

Golimumab, one of the newest TNF antagonists to reach the market, is an appealing treatment option for patients with moderate to severe psoriatic arthritis. Its once monthly home dosing may be attractive to some patients. Golimumab may also be an effective alternative when patients fail treatment with other TNF antagonists.

Disclosures

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