Review Article

Golimumab and certolizumab: The two new anti-tumor necrosis factor kids on the block

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ABSTRACT

Anti-tumor necrosis factor (anti-TNF) agents have revolutionized treatment of psoriasis and many other inflammatory diseases of autoimmune origin. They have considerable advantages over the existing immunomodulators. Anti-TNF agents are designed to target a very specific component of the immune-mediated inflammatory cascades. Thus, they have lower risks of systemic side-effects. In a brief period of 10 years, a growing number of biological therapies are entering the clinical arena while many more biologicals remain on the horizon. With time, the long-term side-effects and efficacies of these individual agents will become clearer and help to determine which ones are the most suitable for long-term care. Golimumab (a human monoclonal anti-TNF-α antibody) and Certolizumab (a PEGylated Fab fragment of humanized monoclonal TNF-α antibody) are the two latest additions to the anti-TNF regimen. Here, we are providing a brief description about these two drugs and their uses.

Key words: Anti-tumor necrosis factor agents, Certolizumab, Golimumab

INTRODUCTION

In the past decade, the synthesis of anti-tumor necrosis factor (anti-TNF) agents has introduced new and innovative methods of treating many immunologic diseases. These medications are designed to target specific components of the immune system and are a major technological advancement over traditional immunosuppressive medications. To date, the Food and Drug Administration (FDA) has approved five TNF-α inhibitors for the treatment of a variety of inflammatory conditions [Table 1].

- Adalimumab – a human monoclonal anti-TNF-α antibody
- Certolizumab pegol – a PEGylated Fab fragment of humanized monoclonal TNF-α antibody
- Etanercept – a soluble p75 TNF-α receptor fusion protein
- Golimumab – a human monoclonal anti-TNF-α antibody
- Infliximab – a mouse/human chimeric anti-TNF-α monoclonal antibody

Golimumab (a human monoclonal anti-TNF-α antibody) and Certolizumab (a PEGylated Fab fragment of humanized monoclonal TNF-α antibody) are the two latest additions to the anti-TNF regimen. Both these medicines were approved by the FDA in the early part of 2009 for rheumatoid arthritis (RA) and are likely to be used for various cutaneous autoimmune diseases. These two drugs are new to our armory for various autoimmune diseases. The purposes of this article are to (1) evaluate the available evidence of safety, tolerability, efficacy and other pharmaceutical issues relevant to the clinicians related to golimumab and certolizumab, (2) define its therapeutic role in autoimmune diseases already approved by the FDA and (3) to identify their potential uses as anti-TNF agents in various cutaneous inflammatory diseases.

TNF-ALPHA: A UNIQUE TARGET MOLECULE FOR THE TREATMENT OF INFLAMMATORY DISEASES

The role of TNF-α (cachexin or cachectin) in the initiation and maintenance of an inflammatory

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Table 1: FDA-approved TNF-α inhibitors and their pharmacological properties

TNF-α Inhibitor	Description	Mechanism	Composition	Half-Life ($t_{1/2}$) (days)	Method of Administration	Dose
Infliximab (Remicade®)	Chimeric (mouse/human) anti-TNF-α antibody	Anti-TNF monoclonal antibody (mAb)	Human and mouse proteins	8–10	Intravenous infusion	• First three doses within 10 weeks • Once every 8 weeks thereafter
Adalimumab (Humira®)	Human monoclonal anti-TNF- antibody	Anti-TNF (mAb)	Human proteins	14	Subcutaneous injection (SQ)	Once every 2 weeks
Etanercept (Enbrel®)	Soluble p75 TNF-α receptor fusion protein	TNF-α soluble decoy receptor	Human fusion protein	4–6	SQ	1–2 times per week
Golimumab (Simponi®)	Human monoclonal anti-TNF- antibody	Anti-TNF (mAb)	Human protein	14	SQ	Once per month
Certolizumab pegol (Cimzia®)	Pegylated Fab fragment of humanized monoclonal TNF-α antibody	Pegylated Anti-TNF (mAb)	Human protein	14	SQ	Once per month

reaction is unquestionable. This pro-inflammatory cytokine is synthesized initially as a transmembrane precursor protein. The major source of TNF are the antigen presenting cells such as activated macrophages and dendritic cells; however, effector T cells also contribute a substantial amount of TNF-α. TNF-α induces apoptotic cell death and inflammation and also inhibits tumor genesis and viral replication. The levels of TNF-α are elevated both locally and systemically in chronic inflammatory diseases such as RA, ankylosing spondylitis, psoriasis and Crohn's disease, suggesting that higher levels of TNF-α may directly contribute to tissue damage.[1-3] TNF-α along with its receptors (TNFR1, TNFR2) regulates critical cellular and molecular events associated with inflammatory cascades of autoimmune diseases. TNF-α stimulates the release of the inflammatory cytokines interleukin (IL)-1 beta, IL-6, IL-8 and granulocyte monocyte colony stimulating factor (GM-CSF). It induces the expression of endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin) and chemokines (MCP-1, MIP-2, RANTES and MIP-1alpha). In addition, at the disease site, TNF-α directly acts on target tissues to induce proliferation or apoptosis and thus participates in remodeling of the connective tissue and epithelial tissue. On the other hand, blocking of TNF-α will also counter these critical processes required for the immunosurveillance of pathologic microbial agents. Thus, it is not surprising that all anti-TNF-α agents have been associated with a variety of serious and "routine" opportunistic infections because they suppress the inflammatory response.[1]

PHARMACOLOGIC PROPERTIES OF GOLIMUMAB AND CERTOLIZUMAB

Golimumab is a fully human anti-TNF-α monoclonal antibody created in specific transgenic mice. Instead of humanizing the mouse antibodies by using phage display technology, recent technologies have allowed for the humanization of the mice. In transgenic mice, the genes coding for the mouse antibody genes can been suppressed and human antibody genes can be inserted.[4] Thus, when the resulting transgenic mouse is immunized with a target antigen, the mouse produces antibodies from the human genes inserted into its genome. Golimumab is made using this technology, with a specific aim to make genetically engineered mice that will make human anti-TNF antibody.[4,5] Golimumab forms high-affinity, stable complexes with human TNF. The action of Golimumab is very similar to that of infliximab, adalimumab and Certolizumab. It acts by neutralizing both circulating and membrane-bound forms of human TNF.[5,6]

Certolizumab is a PEGylated recombinant, humanized antibody Fab' fragment specific for human TNF-α. Certolizumab does not contain an Fc region, unlike infliximab and adalimumab, and does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro*.[7] The pegylation of the antibody delays the elimination and thus provides a longer half-life. As a result of this, the medication may be administered monthly. Certolizumab is the only TNF inhibitor that uses PEGylated technology.

THERAPEUTIC EFFICACY NOTICED IN CLINICAL TRIALS

Therapeutic efficacy of Golimumab (Simponi): In several multicenter, randomized, double-blind, controlled trials, the efficacy and safety of Golimumab have been evaluated.[6,8-13] Safety and efficacy studies have been carried out in RA, psoriatic arthritis (PsA), psoriasis and ankylosing spodylitis. A majority of the studies have been carried out in RA patients, including in early-onset untreated patients. In a recent phase III, multicenter, randomized, double-blind, placebo-controlled study, it has also been reported that in RA Golimumab can be considered as first-line therapy for early-onset RA.[8]

In RA, efficacy and safety data of Golimumab are available from a series of studies denoted as RA-1, RA-2 and RA-3. The RA-1 study is known as GO-AFTER and RA-2 is known as GO-FORWARD.[7,13] These studies were performed in 1,542 patients of ≥18 years of age with moderately to severely active RA.[6,9,10] Double-blinded controlled efficacy data were collected and analyzed through Week 24. In studies RA-1 and RA-2, the patients were allowed to continue low-dose corticosteroids (equivalent to ≤10 mg of prednisone a day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) and patients may have received oral methotrexate (MTX) during the trials.

Study RA-1 evaluated 461 patients who were previously treated (at least 8–12 weeks prior to administration of study agent) with one or more doses of a biologic TNF-blocker without a serious adverse reaction. Study RA-2 evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with a biologic TNF-blocker. Study RA-3 evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with a biologic TNF-blocker.

The primary endpoint in Study RA-1 and Study RA-2 was the percentage of patients achieving an American College of Rheumatology (ACR) 20 response at Week 14 and the primary endpoint in Study RA-3 was the percentage of patients achieving an ACR 50 response at Week 24.[6,9,10] Golimumab was found to be more effective than the placebo and MTX in these trials. The combination therapy of Golimumab and MTX achieved a higher percentage ACR responses at Week 14 (Studies RA-1 and RA-2) and Week 24 (Studies RA-1, RA-2 and RA-3) versus patients treated with MTX alone.[6] There was no clear evidence of improved ACR response with the higher Golimumab dose group (100 mg) compared to the lower Golimumab dose group (50 mg). In the study RA-1, the proportion of patients achieving ACR 20, 50 and 70 responses at Week 14 were 35%, 16% and 10%, respectively, in the Golimumab 50 mg + MTX group (n = 103) compared with 17%, 6% and 2%, respectively, in the placebo + MTX group (n = 107).[6,10]

The safety and efficacy of golimumab have also been evaluated in a multi-center, randomized, double-blind, placebo-controlled trial in PsA. This study was carried out in 405 adult patients with moderate to severe forms of active PsA (≥3 swollen joints and ≥3 tender joints).[6,11] Patients in this study had PsA with a median duration of 5.1 years and with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Previous treatment with a biologic TNF-blocker was not allowed; however, patients could receive methotrexate/oral corticosteroid/NSAID. The primary endpoint was the percentage of patients achieving ACR 20 response at Week 14. In this 24-week double-blind, randomized trial, patients were randomly assigned to placebo, Golimumab 50 mg or Golimumab 100 mg given subcutaneously every 4 weeks. ACR 20 responses at week 14 occurred in 9%, 51% and 45% of the three groups, respectively. At Week 14, at least 75% improvement in the Psoriasis Area and Severity Index (PASI) scores occurred in 3%, 40% and 58%, respectively. There was no clear evidence of improved ACR response with the higher Golimumab dose group (100 mg) compared to the lower Golimumab dose group (50 mg). Similarly, Golimumab has been found to be effective in 356 adult patients with active ankylosing spondylitis.[6,12]

Certolizumab pegol (Cimzia): In RA, efficacy and safety data of Certolizumab are available from a series of studies denoted as RAPID 1, RAPID 2 and FAST4WARD. Certolizumab has been compared to placebo in 1,821 patients with moderate to severe forms of active RA in these multi-center, double-blind, randomized controlled trials. Outcomes of efficacy were determined by percentage of patients achieving ACR 20 response at Week 24. FAST4WARD compared Certolizumab 400 mg every 4 weeks with placebo in RA patients who failed at least one prior disease-modifying antirheumatic drug (DMARD).[14] Patients were randomized into two treatment groups: CIMZIA 400 mg (n = 111) every 4 weeks from baseline to Week

20 and placebo (n = 109) every 4 weeks from baseline to Week 20. The ACR 20 response rate at Week 24 was defined as the primary endpoint of this study. Other outcomes included ACR50 and ACR70 response rates at Week 24 and adverse effects. CIMZIA demonstrated a significant therapeutic response at Week 24. The ACR 20 response rate was higher in patients who received Certolizumab 400 mg (45.5% vs. 9.3%; $P < 0.001$). The secondary endpoints of ACR 50 and ACR 70 were superior to placebo (ACR 50: Certolizumab 22.7% vs. 3.7% [$P < 0.001$]; ACR70: Certolizumab 5.5% vs. 0% [$P \leq 0.05$]). The patient-reported outcomes were also better in the Certolizumab arm. Physical function (HAQ-DI minimal clinically important differences) was defined as a decrease of ≥0.22 points from baseline in the HAQ-DI. More patients in the Certolizumab arm reported physical function improvement (49% vs. 12%; $P < 0.001$). RAPID 1 compared the combination of MTX and Certolizumab to MTX monotherapy in TNF-inhibitor naïve patients with active, uncontrolled RA despite treatment with MTX monotherapy. The primary efficacy outcomes included ACR 20 response rate at Week 24 and total modified Sharp score at Week 52. More patients in the combination treatment arms achieved the primary endpoint of ACR 20 response rate at Week 24. At Week 52, there was a smaller mean change from baseline in the modified total Sharp score in patients who received the combination treatment compared to MTX monotherapy, which indicates less bone erosion and joint-space narrowing. RAPID 2 compared the combination of Certolizumab and MTX with MTX monotherapy in patients with active RA whose symptoms were inadequately controlled with ≥6 months of treatment with MTX monotherapy. Patients (n = 619) were randomized 2:2:1 to subcutaneous Certolizumab pegol (liquid formulation) 400 mg at Weeks 0, 2 and 4 followed by 200 mg or 400 mg plus MTX or placebo plus MTX every 2 weeks for 24 weeks. The results showed that significantly more patients in the Certolizumab pegol 200 mg and 400 mg groups achieved an ACR 20 response versus placebo (P [0.001]). Certolizumab pegol 200 mg and 400 mg also significantly inhibited radiographic progression. Most adverse events were mild or moderate, with a low incidence of withdrawals due to adverse events. Five patients developed tuberculosis.[15]

The efficacy and safety of Certolizumab pegol in the treatment of Crohn's disease was evaluated by randomized, double-blind, placebo-controlled trials (also known as PRECiSE1 and PRECiSE2).[16-18] The results of these studies demonstrated that in moderate to severe Crohn's disease, induction and maintenance therapy with Certolizumab pegol was associated with a modest improvement in response rates as compared with placebo.

INDICATIONS

The FDA has approved Golimumab for RA, PsA and ankylosing spondylitis.[6] More specifically, Golimumab, in combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA. Golimumab, alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA and Golimumab is indicated for the treatment of adult patients with active ankylosing spondylitis.

Certolizumab pegol is approved by the FDA for adults with moderately to severely active RA.[14] Certolizumab pegol is also approved by the FDA for adults with moderate to severe Crohn's disease who have not responded to conventional therapies.

DOSAGE AND ADMINISTRATION

Golimumab is available in 50 mg single-dose pre-filled syringes or autoinjectors. The recommended dose is 50 mg subcutaneously once monthly.

Certolizumab is supplied as a lyophilized powder that requires reconstitution with sterile water (1 cc of water per 200 mg vial) or as a solution of 200 mg/ml (1 ml) and should be administered subcutaneously. Dosage for Certolizumab is as follows:

Crohn's disease: Initial dose is 400 mg, repeat dose 2 and 4 weeks after initial dose; maintenance dose is 400 mg every 4 weeks.

Rheumatoid arthritis: Initial dose is 400 mg, repeat dose 2 and 4 weeks after initial dose; maintenance dose could be 200 mg every other week. Alternatively, a maintenance dose of 400 mg every 4 weeks may also be considered.

ADVERSE EFFECTS

Anti-TNF drugs in general: TNF antagonists are generally safe; however, there has been concerns over the increased risks of atypical and opportunistic

infections, lymphoma and certain autoimmune diseases with the use of these agents. From a public health standpoint, the development of active tuberculosis in some patients who receive TNF-α inhibitor therapy is a matter of serious concern.[1] Clinicians should be vigilant for tuberculosis in patients treated with TNF-α inhibitor agents because tuberculosis in such patients frequently presents as extrapulmonary or disseminated disease. Several reports have indicated a lower risk of developing tuberculosis and other granulomatous infections in patients treated with etanercept compared with monoclonal antibodies infliximab or adalimumab. In a recent review, we have covered in detail these issues along with various preventive measures to reduce the risks of infections associated with anti-TNF therapy.[1]

Golimumab: In clinical trials evaluating the efficacy and safety of Golimumab, the rates of adverse events were 65% in all Golimumab-treated groups and 59% in all placebo-treated groups.[11] The most common adverse events in the Golimumab-treated group were upper respiratory tract infections, nasopharyngitis, liver transaminase elevations and injection site reactions. Elevations of alanine transaminase (ALT) and aspartate transaminase (AST) occurred in 24% and 18% of the patients receiving Golimumab 50 mg, 35% and 10% of the patients receiving Golimumab 100 mg and 18% and 10% of the placebo-treated patients, respectively.[11] Serious adverse events were reported for 2% of all Golimumab-treated patients versus 6% of the placebo-treated patients.

Certolizumab pegol: In clinical trials, Certolizumab was well tolerated. Serious infections, including abscesses, pneumonia and pyelonephritis, occurred in 2.8% of the Certolizumab-treated subjects and 0.9% of the placebo-treated subjects. One Certolizumab-treated patient with a negative purified protein derivative (PPD) skin test at screening developed pulmonary tuberculosis. Four malignancies in PRECiSE 1 (in 662 patients) were reported, two with placebo and two with Certolizumab. In PRECiSE 2 (668 patients), no malignancies occurred. Antinuclear autoantibodies (ANA) turned positive in 3.7% of the Certolizumab-exposed patients and 0.93% in the placebo group in PRECiSE 2, but only one patient in the Certolizumab-exposed group developed a lupus-like syndrome.[19]

SCREENING TESTS FOR TUBERCULOSIS AND OTHER RISK FACTORS BEFORE ANTI-TNF THERAPY

Although TNF-α blockers are generally well tolerated, physicians need to be extremely cautious about the potential of serious side-effects of anti-TNF drugs and should review the indications/contraindications of anti-TNF agents in every patient [Table 2]. The existence of any contraindications to the use of these agents [Table 2] needs to be considered before the commencement of therapy. In patients receiving TNF-α inhibitors, an increased risk of reactivation of latent tuberculosis infection (LTBI) is now an established fact. The Centers for Disease Control and Prevention recommend pre-screening of all patients for LTBI prior to starting a TNF-α inhibitor.[20] Screening recommendations for tuberculosis include a full medical history, physical examination, Mantoux test or tuberculin skin test (TST) or interferon-gamma release assay (IGRA)/*QuantiFERON®-TB* and a chest radiograph in those with a positive TST or IGRA. The IGRA or the *QuantiFERON®-TB test* can also be used to distinguish a true Mantoux test from a false-positive test caused by BCG sensitization.[21-23] However, the rates of indeterminate IGRA results are higher in patients with RA.[22]

The conditions mentioned in Table 2 should be scrutinized in each person and specific attention should be given to evaluate other occult infections such as hepatitis and human immunodeficiency virus. In the Indian subcontinent, reactivation of tuberculosis or new tuberculosis infection following anti-TNF agents is a very serious concern. Rheumatologists and dermatologists in India are aware of this issue and are working on a specific project to have a protocol that will allow appropriate use of anti-TNF and other biologics and provide a proper protocol for tuberculosis screening for anti-TNF therapy (personal communication). Additional studies are needed as official recommendations vary depending on each

Table 2: Contraindications for the use of TNF-α blockers

Absolute
Untreated TB
Active infections (including infected prosthesis, severe sepsis)
History of recurrent or chronic infections (e.g., bronchiectasis)
Congestive cardiac failure (moderate to severe)
Multiple sclerosis or optic neuritis
Active or recent history (past 10 years) of malignancy except for skin cancer
Relative
Pregnancy
Lactation
HIV, hepatitis B, hepatitis C infection

country and their incidence rates of tuberculosis and vaccination. No official guidelines currently exist for many other opportunistic infections. However, for certain geographic areas, screening for histoplasmosis and coccidioidomycosis has been suggested.[1]

Here, we will briefly discuss the current recommendations about screening test for TB before initiation of anti-TNF therapy. A PPD of 5–9 mm is considered positive for those with epidemiologic risk factors and 10 mm or greater for all others. PPD criteria for those who are about to begin or have already begun TNF-α therapy is an important issue.[24] With regards patients receiving TNF-α inhibitors, Crum *et al*. recommend following the American Thoracic Society guidelines for patients with immunosuppressive conditions.[25] They consider a PPD positive with ≥5 mm and recommend consideration of latent tuberculosis therapy as per the suggestions of Gardam *et al*.[24,25]

Despite clinical evaluation and Mantoux test screening, tuberculosis still appears to be higher for patients on TNF-α inhibitor therapy than for the general population.[26] It has been proposed that irrespective of the PPD result, i.e. even if PPD is 0–4 mm, patients receiving TNF-α inhibitors and other immunosuppressive agents, who have a chest X-ray consistent with old tuberculosis or recent contact with an active tuberculosis case, should be treated for latent TB.[24] However, screening for tuberculosis is an important measure. A very encouraging observation has been noted in a study of the Spanish registry of patients with rheumatic disease treated with TNF-α inhibitors, BIOBADASER, wherein a 74% reduction in the tuberculosis case rates has been observed following the introduction of screening and treatment in patients with RA treated with infliximab.[26]

CONCLUSION

Golimumab is produced in genetically engineered mice that make human anti-TNF antibody. Thus, theoretically, Golimumab has the potential to be less immunogenic compared to the other humanized antibodies such as infliximab and adalimumab. Golimumab (Simponi) appears to be effective in the treatment of RA (with MTX), PsA and ankylosing spondylitis.[6,13] However, there are no clinical trials available comparing the efficacy, tolerability and adverse reactions of Golimumab vs. other anti-TNF drugs.[8-12,27,28] The once-monthly injection schedule of Golimumab provides a more convenient dosing regimen.

Certolizumab pegol (Cimzia) is effective in the treatment of moderately to severely active RA. Certolizumab pegol (Cimzia) has produced modest rates of response and remission in patients with moderate to severe Crohn's disease, including some previously treated with infliximab (Remicade).[16,18] Patients who respond to the drug appear to benefit from continuing on maintenance treatment.[17] In Crohn's disease, it has the advantage over infliximab of subcutaneous rather than intravenous administration and the advantage over adalimumab (Humira) of maintenance dosage every 4 weeks rather than every 2 weeks.[17,18] Certolizumab differs from other TNF inhibitors, in that it lacks the Fc portion of the antibody and the Fab' portion is bound to PEG. Potential benefits of this technology include less immunogenicity and longer half-life. A less immunogenic product may mean that less neutralizing antibodies will develop and therefore not require more frequent dosing. How certolizumab compares in efficacy and safety with other TNF blockers remains to be established.

Anti-TNF preparations have provided a new dimension in the treatment of severe forms of psoriasis. Various reports suggest that anti-TNF could be very effective in inflammatory skin diseases like Behcet's disease, pyoderma gangrenosum, cutaneous Chron's disease and subcorneal pustular dermatitis.[29,30] It is expected that like other anti-TNF agents, Golimumab and Cetrolizumab will be used for psoriasis and other inflammatory cutaneous diseases. The long-term risk of malignancy or serious infection with all of these drugs is still unclear. Overall, there is no clear distinguishing difference in the safety and efficacy profiles among the currently available five anti-TNF agents. The choice will depend more on cost and convenience of the patient.

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Multiple Choice Questions

1. Screening for hepatitis is not required before initiating therapy with:
   a. Anti-TNF agents
   b. Rituximab
   c. Methotrexate
   d. Hydroxychloroquine

2. Major source of TNF in a psoriasis lesion is:
   a. Activated T cells
   b. CD8+ T cells
   c. Antigen presenting cells
   d. Keratinocytes

3. Which of the following anti-TNF agent can be given subcutaneously as a monthly dose?
   a. Golimumab
   b. Certolizumab
   c. Golimumab and Certolizumab
   d. Infliximab and Certolizumab

4. Among the anti-TNF agents, the risks of reactivation is least in:
   a. Etanercept
   b. Golimumab
   c. Certolizumab
   d. Infliximab

5. Which agent may not require PPD screening before therapy:
   a. Etanercept
   b. Methotrexate
   c. Rituximab
   d. Adalimimab

6. All of the following monoclonal anti-TNF antibodies have an Fc portion except:
   a. Golimumab
   b. Infliximab
   c. Certolizumab
   d. Adalimumab

7. Pegylation of an antibody is a useful method to:
   a. Increase the half-life of a drug
   b. Increase renal excretion
   c. Reduce risks of reactivation of pulmonary TB
   d. Reduce drug toxicity

8. Which of the biologics is a PEGylated antibody?
   a. Infliximab
   b. Rituximab
   c. Abatacept
   d. Certolizumab

9. All of the following are recognized side-effects of anti-TNF agents except:
   a. Reactivation of TB
   b. Pyoderma gangrenosum
   c. Exacerbation of CHF
   d. Psoriasis

10. Golimumab is indicated for:
   a. Psoriatic arthritis
   b. Pemphigus
   c. Lupus
   d. Crohn's disease

Answers

1. d, 2. c, 3. c, 4. a, 5. b, 6. c, 7. a, 8. d, 9. b, 10. a