*REVIEW ARTICLE*

*INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE*

*A Path for Horizing Your Innovative Work*

# GOLIMUMAB: A HUMAN MONOCLONAL ANTIBODY AGAINST TUMOUR NECROSIS FACTOR-α FOR THE RHEUMATOID ARTHRITIS: AN OVERVIEW

***DHARAK SHAH, KAMAL MODH, I. S. ANAND**

Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001Gujarat, India

Corresponding Author Email: dharakshah1989@gmail.com

**Accepted Date: 25/04/2012** **Publish Date: 27/04/2012**

**Abstract:** Golimumab is a new approved human monoclonal antibody for the treatment of rheumatoid arthritis (RA). It was approved in the United States in 2009. This antibody is used against pro-inflammatory cytokine tumour necrosis factor –α. Golimumab is subcutaneously administered with MTX or not using MTX. Golimumab is administered as 50-mg subcutaneous injection once a month. The most common adverse effects include injection site erythema, headaches, and nausea.

**Keywords:** Arthritis, Rheumatoid, TNF-α, Golimumab.

## *INTRODUCTION*

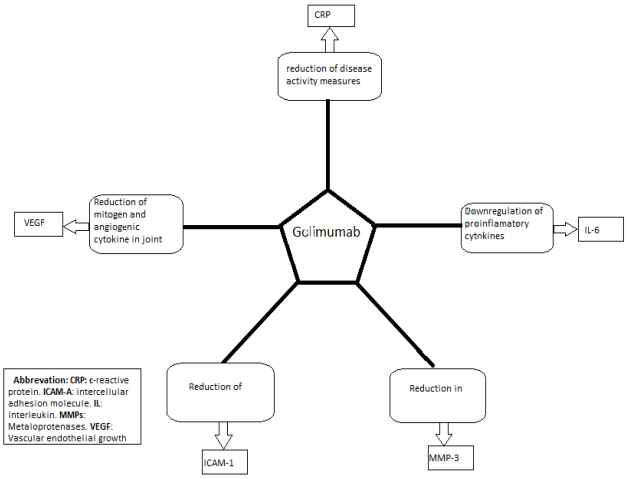
Rheumatoid Arthritis (RA) is an autoimmune disease associated with the chronic inflammation in the synovial joints[1]. Synovial inflammation damages cause bone erosion, which can result in the diminished joints irregularities. It is associated withjoint destruction seen within 6 months of disease onset[2], to bone erosion.[3], and to an increased disability associated with a reduced health related quality of life[4]. RA pathophysiology can be explained by Tumour necrosis factor-α (TNF-α, cachexin or cachetin). This cytokinin deriving from monocytes/macrophage lineage, T lymphocytes and β lymphocytes, neutrophils, mast cells and also from non-immune cells[5,6] is found in high concentration in the synovial compartments of patients with RA[7,10]. Moreover it choreographs not only the synthesis of the other pro-inflammatory cytokines such as interleukin (IL)-1 IL-6, granulocyte macrophage colony stimulating factor. Synthesis of especially of IL-1 and IL-6, TNF-α inhibits proteoglycan synthesis in the cartilage[11]. Furthermore TNF-α is in the origin of the cell, recruitment in the joints by leucocyte infiltration and migration enhancement through up regulation of adhesion molecule such as intercellular adhesion molecule-1 (ICAM-1), and through endothelial permeability increases[12, 13]. Finally, TNF- α stimulates the activation of osteoclasts and also some metalloproteinase (MMP) conducting to bone erosion [14].

TNF-α functions blocking will logically treat RA disease. Many clinical studies, using these TNF-α blockers, have demonstrated a dramatic disease improvement[15], a rapid reduction in joint damages[16], and a rapid decrease in cellularity at the inflammation site[17]. If we block TNF-α it will play an immunomodulatory effect causing improvement in patients life quality [15].The presence of TNF-α blockers in cells culture derived from diseased joints inhibits many pro-inflammatory cytokines[5, 6, 18].they remarkably down regulate degradative enzymes such as MMP-3, angiogenic cytokines like the vascular endothelial growth factor and the expression of the adhesion molecules reducing leucocyte migration into joints and probably reducing synovial inflammation[17] Fig-1.

Because all the patients have not same response to these blockers, many TNF-α blockers were developed[19, 20]. Nevertheless, only five TNF-α blockers are approved by the USA Food and Drug administration (FDA) and are currently available. Chronologic order of this

approval for RA treatment is follows: Infliximab, Etanercept, and Adalimumab. Golimumab and Gertolizumab pegol.

These agents can be divided into two groups. The first one is constituted from antibody to TNF-α (Infliximab, Adalimumab, Golimumab, and Certolizumab pegol), and the second one is constituted from TNF-α receptors linked to Fc domains (Etanercept). All these agents share the same function, which is triggering and specifically inhibiting soluble trimeric TNF-α and/or its transmem-branous form[20]. Infliximab is the only chimeric mono-clonal anti-TNF-α antibody (cA2, Remicade, Centocor Ortho Biotech, Horsham, PA, USA). This antibody is used to treat different diseases comprising RA disease (USA FDA) Approval in August 1998)[21].The Adalimumab (D2E7, Humira, Abbott Park, IL, USA), has been discovered and approved by USA FDA in Dec. 2002 for the RA treatment[22]. After this antibody, which has not been associated, as expected, with dramatic and massive reduction of human anti-biologic TNF-α blockers, Certolizumab pegol and Golimumab were discovered. Gottolizumab pegol (CDP870, Cimzia, UCB Inc., Smyrna, GA, USA FDA approval for RA treatment in May 2009) is a polyethyleneglycolated humanized antibody anti-TNF-α that has clearly proved prolonged half-life owing to its PEG fragment[23].



Multifunctions of Golimumab, CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; MMPases, metalloproteinase; VEGF, Vascular endothelial growh factor.

## HISTORY OF GOLIMUMAB

Golimumab (CNTO148, Simponi™, centocor ortho biotech Inc, USA FDA approval for RA treatment in April 2009) is a fully human antibody raised against TNF-α. Golimumab is indicated for the treatment of active RA, alkylosing spondylitis (AS) [24], and psoriatic arthritis (PA) [25, 26] This antibody produced by Jonhson & Jonhson's subsidiary centocor ortho biotech of Horsham, Pennsylvania, and shering-Plough of Kenilworth, New JERSY[27], has demonstrated, as expected low immunogenicity because only 6.5% of patients have developed HAHA andonly 21% of patients developed autoantibodies such as anti-nuclear antibodis (ANA) with non-severe adverse effects[28].

**Chemical Name:** Disulphide with human monoclonal CNTO 148 k-chain anti-(human tumour necrosis factor a) (human monoclonal CNTO 148 g1-chain) immunoglobulin G1 dimer.

**Molecular formula**: $C_{6530}H_{10068}N_{1752}O_{2026}S_{44}$

## INDICATION

The golimumab is approved only for adults having age of greater than 18[29], with moderate to severely active RA after subcutaneous injection in a dose of 50 mg once a day[12, 30]**.** It is intended in the use of combination with methotrexate (MTX) for RA treatment and with/without MTX or other non-biologic disease-modifying antirheumatic drugs and/or NSAID for PA and AS. The MTX is an antimetabolite drug administered in low dosage. It rapidly interfere with purine and pyrimidine synthesis which inhibit the activation of T lymphocytes and the function of granulocyte[31].

## DOSAGE AND ADMINISTRATION

The FDA- approved dose for all of these condition in 50mg injected subcutaneously once in the month. It is available as simponi and manufactured by centocor ortho/biotech inc. golimumab is available in 2 single use forms: a pre filled syringe and a prefilled smart ject autoinector. It is provided in one strength, 50mg/0.5 ml, and does not contain preservatives. The solution is clear light yellow, with a ph of about 5.5 for the autoinjector, patients should be inject at 90-degree angle, whereas the prefilledsyringes should inject at 45-degree angle. For the prefilled syringe, patient should not pull back on the plunger after inserting. Recommended places for injection are the front middle thighs, lower

abdomen or outer upperars. Goimumab must be protected from light and refrigerated prior to use and he injection should be placed at room temperature 30 min prior to administration[32].

## MECHANISM OF ACTION

Golimumab is a human monoclonal antibody. Golimumab binds to both the soluble and Trans membrane bioactive forms of human TNF-α.Because of interaction of golimumab there will be no interaction of TNF-α to its receptors, takes place. This interaction prevents the biological activity of TNF-α (a cytokine protein). There was no evidence of the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab antibody did not bind or neutralize human lymphotoxin[33].

Elevated TNF-α level in the blood, synovium, and joints have been implicated in the pathophysiology ofchronic RA.Golimumab modulated the in vitro biological effects mediated by TNF in several bio assays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, inter cellular adhesion molecule [ICAM]- 1 and vascular cell adhesion molecule-1) and the secretion of proinflammatory cytokines (interleukin [IL]-6, IL-8, G-CSF and GM-CSF)[34,35]

## PHARMACOKINETICS AND PHARMACODYNAMICS

### PHARMACOKINETICS PROPERTIES

Following the subcutaneous (SC) administration of Golimumab to healthy subjects and patients with active RA, the median time to reach maximum serum concentrations (Tmax) ranged from 2 to 6 days. A SC injection of 50 mg golimumab to healthy subjects produced a mean maximum serum concentration of approximately 2.5 µg/ml. Golimumab exhibited dose-proportional pharmacokinetics in patients with active RA, over the dose range of o.1 to 10.0 mg/kg following a single intravenous (IV) dose. Following a single IV administration in patients with RA, mean systemic clearance estimated at 4.9 to 6.7 ml/day/kg and mean volume of distribution ranged from 58 to 126 ml/kg.

When 50 mg golimumab is administered SC to patients with RA every 4 weeks, serum concentration appeared to reach steady state by week 12. With methotrexate (MTX), golimumab SC every 4 weeks resulted in a mean steady state through serum concentration of approximately 0.4-0.6 µg/ml in patients with active RA. Patients with RA and methotrexate

have approximately 52% higher mean steady-state through concentration of

golimumab, respectively compared with golimumab 50 mg without MTX. Pharmacokinetic analyses indicated that concomitant use of NSAIDs, oral corticosteroid, or sulfasalazine did not influence the apparent clearance of golimumab. The presence of MTX decreased anti-golimumab antibody incidence from 7% to 2%[32].

## PHARMACODYNAMICS PROPERTIES

Golimumab inhibits soluble and Trans membrane forms of TNF-α binding to their specific receptor and blocking in consequence their bioactivity[36]. Golimumab neither bind nor inhibit other members of TNF-α such as lymphotoxin (TNF-β). Following golimumab therapy, numerous positive responses related to RA disease cure were obtained, such as reductions in level of c-reactive protein (CRP), IL-6, MMP-13, ICAM-1&VEGF[12].

## ADVERSE EFFECTS

The safety of golimumab was assessed previously mentioned trials. Over all, the drug was well tolerated[37-40]. In all the published phase 2 or 3 clinical trials .one patient developed tuberculosis and 2 patients developed lymphoma while on golimumab therapy. The most common adverse effect associated with golimumab was nausea and injection site reactions. Erythema was the most common injection site reaction. Patients receiving golimumab must be monitored closely and therapy should be stopped if a patient develops an infection.

## SPECIAL WARNING AND PRECAUTIONS FOR USE

## PRECAUTIONS AND CONTRAINDICATION

As with other TNF-α inhibitors, GLM should not be used – or should be used cautiously, in patients with active infection, heart failure, demyelinating disease, or a history of tuberculosis or hepatitis B infection. Use of GLM should be stopped if patients develop serious infections, reactivation of latent infection (e.g., tuberculosis, hepatitis B), or exacerbation or new onset of demyelinating disease. Based on the finding that GLM was associated with exacerbation of asthma in a study in patients with severe asthma[41], patients with asthma should be monitored closely if they begin taking GLM. In addition, patients with latex allergy should not touch or be exposed to the needle cover on the prefilled GLM syringes[42].

## DRUG INTERACTIONS

Due to the higher risk of infection when TNF- an inhibitors are used with anakinra

and/or abatacept, this combination should be avoided. Also the patients should not receive live virus vaccinations while being treated with golimumab. It is possible that, at initiation of golimumab, cytochrome p450 enzymes that have been suppressed may normalize. Therefore, medications metabolize through the p450 pathways, especially if they if they have narrow therapeutic windows, should be monitored closely during initiation or discontinuation of golimumab[43].

**THERAPEUTIC-ECONOMIC ISSUES AND CONTROVERSIES**

Unfortunately no current data can compare the TNF- a inhibitors to one another. However, a meta-analysis published by Alonso-ruiz et al. analysed the effects of the 3 original TNF-a inhibitors for RA. For overall effects of 3 medications compared with the control, the relative risk(95% cl) of response for ACR20 was 1.81(1.43to2 .29); for ACR50, 2.6(1.75 to 3.45); and for ACR70, 2.77(1.85 to 4.15) data from the GO-FORWARD and from GO-BEFORE trials were used to calculate relative risk and confidence intervals for response rates used to calculate relative risk and confidence intervals for response rates at 24 weeks in patients receiving the golimumab 50-mg monthly dose compared with the control group .Although a statistical result cannot be determined from this data it appears that golimumab is similar in efficacy to the other TNF-a in inhibitors and does not seem to offer a large benefit.

There are no economical comparisons to studies, but the cost of the biologic agents used to treat RA is significant[44] .one advantage of golimumb is there are minimal administration costs since it can be self-administered subcutaneously and there are no infusion related costs. However, etanercept and adalimumab can also be self-administered but must be administered more frequently.

Currently, with 4 TNF-inhibitors on the market, it will be of interest to golimumab's manufacturer to determine the benefits of its drug compared with those of the others of the class. There are no on-going trials comparing golimumab to any other TNF-inhibitors. The most promising data are from the GO-AFTER trial[45], which showed that golimumb is effective after patients have failed other TNF-inhibitors.

## *REFERNCES*

1. Sturrock RD: Update on the pathogenesis of rheumatoid arthritis. Int Conger Ser 2006; 1295: 1-8.

2.Breedveld FC. Weisman MH and Kavanaugh AF: The PREMIER Study A multicenter, randomized, double-blind clinical trial of combination therapy with Adalimumab Plus Methotrexate versus Methotrexate alone or Adalimumab alone in patients with early, aggressive Rheumatoid Arthritis who had not had previous Metho.

3.Aazuma Y, Kaji K, Katogi R, Takeshita S and Kudo A: Tumor necrosis factor-alpha induces differentiation of bone resorption by osteoclasts. J Biol Chem 2000; 275: 4858–64.

4. Lillegraven S and Kvien TK: Measuring disability and quality of life in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007; 21: 827–40.

5. Feldmann M and Maini RN: Anti-TNF alpha therapy of theumatoidarrtitis; what have we learned. Anna Rev Immanol 2001:19:163-96.

6. Toussirot E and Wendling D: The use of TNF-alpha blocking agents in rheumatoid arthritis; an overview. Export Open Pharmactober 2004; 5:1-14.

7. Taylor PC, Peters AM and Paleolog E: Reduction of chemo kine levels and leukocyte traffic to joints by tumor necrosis factor alpha blockade in patients with rheumatoid arthritis. Arthritis Rheum 2000:43:38-47.

8. Sarzi-Puttinia P, Arzenia F. Shoenfeldb Y and Fetraccioli G: TNF-alpha, rheumatoid atthritic, and heart failure a rheumatologic dilemma. Antoimmnn Rev 2005; 4:153-61.

9. Wordsworth P and Holden W: Rheumatoid Arthritis. In: John Wiley & Sons, ed. Encyclopedia of Life Sciences. Chichester: Wiley-Blackwell, 2005; http:// www. els.net / doi: 10: 138/ npg.els. 0004113 (accessed on 7 June, 2010)

10. Moreland LW and Curtis JR: Systemic no articular manifestations of rheumatoid arthritis: focus on inflammatory mechanisms. Sonin Aretbritis Rbeum 2008:39:132-43.

11. Saklatvala J: Tumor necrosis factor alpha stimulates resorption and inhibits

synthesis of proteoglycan in cartilage. Nature 1986; 322:547.

12. Food and Drug Administration. FDA labeling information.FDA web site on line http//www.accessdata.fda.gov/drugsatfda_docs/label/2009/125289s000lbl.pdf.2009

13. Raychaudhari SP, Nguyen CT, Raychaudhauri SK and Gershwin ME: Incidence and nature of infectious disease in patients treated with anti-TNF agents. Autoimmune Rev 2009; 9:67-81.

14. Krane SM, Conca W, Stephenson ML. Amento OP and Golding MB. Mechanisms of matrix degration in rheumatoid arthritis.

15. Smolen JS and Weinblatt ME: when patients with rheumatoid arthritis fail tumor necrosis factor inhibitors.

16. Geokoop-Ruiterman YPM, de Vries-Bouwstra JK and Allart CF: Clinical and radiographic outocomes of four different treatment strategies in patients with RA.

17. Gerlag DM and Tak PP: Novel approaches for the treatment of RA, lessons from the evaluation of synovial biomarkers in clinical trials. Best PractClinRbenmatol 2008; 22:311-23.

18. Brennan FM, Chantry D., Jackson A, Maini R and Feldmann M: Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in RA.

19. Zidi I, Mestiti S, Bartegi B and Ben Amor N: TNF-alpha and its inhibitors in cancer, Med Oncol 2009: DOI: 10:1007/s12032-009-9190-3.

20. Pappas AD, Bathon JM, Hanicq D, Yasothan U and Kirkpatrick P: Golimumab.

21. Elliott MJ, Maini RN and Feldmann M: Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha.

22. Keystone E and Haraoui B: Adalimumab therapy in rheumatoid arthritis and Rheumatism. Rbenm DIs ClinNortb Am 2004; 30:349-64.

23. Edwrads CKI: PEGylated recombinant human soluble tumour necrosis factor receptor type I (r-Hu-sTNF-RI): novel high affinity TNF receptor designed for chronic inflammatory diseases.

24. Inman RD, Davis JJC and van der Heijde D: Efficacy and safety of Golimumab in patients with ankylosing spondylitis: results of a randomized, double-Blind, placebo-controlled, phase III trial. Arthritis Rheum 2008; 58: 3402–12.

25. Hutas G: Golimumab, a fully human monoclonal antibody against TNF-alpha. Curr Opin Mol Ther 2008; 10: 393–406.

26. Kavanaugh A. Melnnes I and Mease P: Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection.

27. Netterwald J. TNF-blocker triple approval Nat Brotecbnal 2009; 27:495.

28. Smolen JS, Kay J and Doyle MK: Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor & inhibiters.

29. Food and Drug Administration. Simponi REMS. FDS web site on line, http://www.fda.gov/downloads/safety/Med. Watch/safety information/safety altersforhuman medical products.

30. Food and drug administration. FDA web site online, http://www.fda.gov/Newsevents/newsroom/PressAnnuncemenys/ucm149569, htm.2009.

31. Caporali R, Caprioli M, Bobbio-Pallavicini F and Montecucco C: DMARDS and infections in rheumatoid arthritis. Autoimmun Rev2008; 8:139–43.

32. Simponi™ (golimumab) [prescribing information], Malvern,pa: centocorortho biotech Inc.

33. Cronstein BN: Molecular therapeutics: methotrexate and its mmechanism of action.Arthritis Rhum 1996; 39: 1951-60.

34. Cutolo M, Sulli A, Pizzroni C, Serilolo B and Straub R: Anti-inflammatory mechanism of methotrexate in rheumatoid arthritis. Ann. Rhum Dis 2001; 60:729-35.

35. Darlymple JM, StamLk, o'DonnellJl and Chapman PT: Pharmacokinetics of oral methotrexate inpatients with rheumatoid arthritis. Arthritis Rheum; 2008; 58; 3299-308.

36. Shealy D, Cai A, Lacy E and Nesspor T: Characterization of golimumab (CNTO 148), a novel fully human monoclonal antibody specific for human TNF-α. Ann rheum Dis 2007; 66 (supply, 2):ii151.

37. Kay J, Matteson EL and DasguptaB: Golimumab in patients with active rheumatoid arthritis despite treatment with rheumatoid arthritis Rheum 2008; 58: 964-75.

38. Keystone EC, Genovese MC and Klareskog L: Golimumab a human antibody to tumornecrosis factor alpha given by monthly subcutaneous injection, in active rheumatoid arthritis despite methotrexate therapy: Ann Rheum Dis 2009; 68 789-96.

39. Emery P and Fleischmann RM: Golimumab a human antibody to human necrosis factor alpha given by monthly subcutaneous injection, in active rheumatoid arthritis every four weeks in

methotrexate-native patients with active rheumatoid arthritis. 2009; 60:2272-83.

40. Smolen J, Kay J and Doyle MK: Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors. Lancet 2009; 374:210-21.

41. Wenzel SE, Barrens PJ and bleckeer ER: for the TO3 asthma investigators. A double blind, randomized, placebo controlled study for the tumor necrosis factor alpha blockade in the severe persistent asthma, Am J Respircrit care MED. 2009;179-549-558.

42. Simponi [package insert]. Horsham, pa: centocorortho biotech Inc; April 2009. Http://www.simponi.com/sites/default/foles /hcp-files/pdf/prescribing-information. August 31, 2010.

43. Product information. Simponi (golimumab) horshan, PA: Centocorortho biotech Inc. April 2009.

44. Cardinal health, Average wholesale price; **2009** August. WWW. Cardinal.com (accessed 2009 Aug 8).

45. Smolen J, Kay J and Doyle MK: Golimumab in patients with active rheumatoid arthritis aftertreatment with tumor necrosis factor alpha inhibitors (Go-after study): a multicenter, randomized, double-blind, placebo-controlled, phase III trial. Lancet 2009:374:210-21.