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GOLIMUMAB

Rec INN; USAN

Human Anti-TNF-α Monoclonal Antibody
Treatment of Inflammation

CNTO-148
Simponi™

Immunoglobulin G_1, anti-(human tumor necrosis factor-alpha) (human monoclonal CNTO 148 γ_1-chain), disulfide with human monoclonal CNTO 148 κ-chain, dimer

CAS: 476181-74-5
EN: 334585

ABSTRACT

Golimumab (CNTO-148, Simponi™) is a new human monoclonal antibody under development by Centocor that targets and neutralizes the proinflammatory cytokine TNF-α. This review summarizes in vitro and in vivo publications and highlights the clinical efficacy and safety data presented to date (i.e., the GO-REVEAL, GO-RAISE, GO-FORWARD and GO-AFTER trials). These clinical findings have led to the recent approval of golimumab in Canada and the U.S. as a once-monthly s.c. treatment for adults with moderate to severe active rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. A request for European approval has recently been submitted. Clinical trials are also under way in ulcerative colitis.

BACKGROUND

The advent of monoclonal antibody (mAb) therapy introduced promising new targeted strategies for several disease states (1). Golimumab (CNTO-148) is a new human mAb candidate developed by Centocor (now Centocor Ortho Biotech) that targets and neutralizes the proinflammatory molecule TNF-α, which can cause inflammation and chronic damage to bones, cartilage and tissue. It has been approved in Canada and the U.S. as a once-monthly s.c. treatment for adults with moderate to severe active rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis under the brand name Simponi™ (marketed by Johnson & Johnson, the parent company of Centocor) (2, 3). Johnson & Johnson has also requested approval from the European Medicines Agency (EMEA) for the use of golimumab as a therapy for those indications approved in the U.S. and Canada (4). It has been reported that, following regulatory approvals, Schering-Plough will assume exclusive marketing rights outside the U.S., except in Japan, Indonesia and Taiwan, where Simponi™ will be comarketed by Mitsubishi Tanabe Pharma and Janssen Pharmaceutical Kabushiki Kaisha, in Hong Kong, where Simponi™ will be exclusively marketed by Janssen-Cilag, and in China, where Simponi™ will be exclusively marketed by Xian-Janssen (3). Table I provides an up-to-date summary of clinical trials for golimumab in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, asthma and ulcerative colitis (5-16).

PRECLINICAL PHARMACOLOGY

Immunoassays have deduced that golimumab has 98% and 100% homology, respectively, to human $IgG_{1κ}$ antibodies specific for human TNF-α (IGHV3-30-3 [heavy chain] and IGKV3-11 [light chain], respectively). Binding studies have also shown that the affinity of golimumab for human TNF-α is 17 pM by surface plasmon resonance and 1.4 pM in solution. The apparent dissociation constant (K_d) for golimumab binding to cells expressing transmembrane TNF was 0.14 nM. In several bioassays, 50% inhibition of TNF-α activity was achieved with an equimolar concentration of golimumab (17, 18).

In vivo studies in a TNF transgenic mouse arthritis model have shown that a single injection of golimumab can reduce histological evidence of joint degradation. Furthermore, in a humanized mouse model of psoriasis, a dose-dependent effect for golimumab has been observed, with a significant reduction in epidermal thickness seen at a dose of 2 mg/kg (95.0 ± 19.9 mm vs. 176.8 ± 28.1 mm; P = 0.003) and Ki-67 labeling (as a marker of cellular proliferation) versus control mice (17).

In vivo investigations also established the effect of golimumab on defects in the development of the neonatal immune system in macaques. Following twice-weekly s.c. injections of golimumab (25 or 50 mg/kg) in utero and postnatally, assessment of the fetal and offspring immune systems demonstrated that golimumab has no effect on T- and B-cell populations in blood and lymphoid tissues and does not impair the ability of the infants to mount an immune response to antigen challenge (19).

PHARMACOKINETICS AND METABOLISM

The population pharmacokinetics of golimumab were evaluated in a randomized, double-blind phase III trial in patients with rheumatoid arthritis. Analysis of serum golimumab samples via NONMEM from 315 patients after 24 weeks of treatment (50 or 100 mg golimumab

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Table I. *Summary of clinical trials for golimumab.*

Condition	Phase	Organization(s)	Status	Location	Ref.
Rheumatoid arthritis	III	Centocor Schering-Plough	Ongoing, but not recruiting participants	US	5-8
	II/III	Janssen Pharmaceutical K.K. Mitsubishi Tanabe Pharma	Recruiting participants	Japan	9
	II/III	Janssen Pharmaceutical K.K. Mitsubishi Tanabe Pharma	Ongoing	Japan	10
Ulcerative colitis	II/III	Centocor Schering-Plough	Suspended	US	11
	II/III	Centocor Schering-Plough	Recruiting	US	12
	III	Centocor Schering-Plough	Recruiting	US	13
Psoriatic arthritis	III	Centocor Schering-Plough	Ongoing, but not recruiting participants	US	14
Ankylosing spondylitis	III	Centocor Schering-Plough	Ongoing, but not recruiting participants	US	15
Asthma	II	Centocor	Terminated	US	16

alone or in combination with methotrexate [MTX]) have shown that a one-compartment pharmacokinetic model with first-order absorption and elimination best describes the observed concentration-versus-time data. Intersubject variability was seen for apparent clearance (CL/F), apparent volume of distribution (V/F) and absorption constant (41.7%, 48.9% and 86.3%, respectively), with weight, concomitant use of MTX, antibody-to-golimumab status and baseline C-reactive protein (CRP) identified as significant covariates (20, 21).

The pharmacokinetics of i.v. golimumab were assessed in another group of patients with rheumatoid arthritis. Single infusions of 0.1, 0.3, 1, 3, 6 or 10 mg/kg golimumab or placebo were analyzed via NONMEM (N = 36). Both the maximum serum concentration and the area under the serum concentration–time curve (AUC) appeared to increase in a dose-proportional manner and a two-compartment population pharmacokinetic model was applied to describe the pharmacokinetics of golimumab. The following parameters were reported in this study: median half-life = 7-20 days; clearance = 0.40 L/day; volume of distribution = 3.07 L (central compartment) and 3.68 L (peripheral compartment); and intercompartmental clearance = 0.42 L/day. Intersubject variability of these pharmacokinetic parameters ranged from 25.5% to 44.6% (residual variability 15%) (22, 23).

The population pharmacokinetics of golimumab were further characterized in patients with psoriatic arthritis from the GO-REVEAL study. Analysis of serum golimumab samples collected through week 24 from 337 patients identified a one-compartment pharmacokinetic model with first-order absorption and elimination, to describe the observed concentration-versus-time data. Intersubject variability in CL/F and V/F was 37.6% and 37.9%, respectively. Of all the covariates tested, weight, antibody-to-golimumab status, baseline CRP and smoking status were identified as significant covariates for CL/F. Weight was also a significant covariate for V/F. The use of concomitant medication (MTX, oral corticosteroids and nonsteroidal anti-inflammatory drugs [NSAIDs]) examined was not found to be a significant covariate for golimumab CL/F (24).

CLINICAL STUDIES

Psoriatic arthritis

The efficacy and safety of golimumab in psoriatic arthritis were investigated in the GO-REVEAL (Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody) study. Data analyzed after a maximum of 52 weeks of s.c. placebo (n = 113), golimumab 50 mg (n = 146) or golimumab 100 mg (n = 146) given every 4 weeks indicated that golimumab significantly improved signs and symptoms of psoriatic arthritis at 24 and 52 weeks (52-week data based on n = 102). American College of Rheumatology (ACR) 20 data (proportion of subjects achieving a 20% improvement in tender or swollen joint counts, as well as 20% improvement in three of the other five criteria [25]) also indicated superior effects for golimumab versus placebo: 12.4% for placebo vs. 52.1% for golimumab 50 mg and 61.0% for golimumab 100 mg at week 24, with further enhancement of this parameter for those on active treatment at 52 weeks (78.4% and 74.1%, respectively, on 50 and 100 mg). Serious adverse events (SAEs) were reported in 6.2% and 2.4% of patients on placebo and golimumab, respectively (26).

The effect of golimumab on psoriatic nail changes and enthesitis was assessed in patients with active psoriatic arthritis. In the GO-REVEAL study (described above) it was evident that the target Nail Psoriasis Severity Index (NAPSI) median percent change from baseline at week 24 was significantly greater for both golimumab 50 mg (33%) and golimumab 100 mg (54%) versus placebo (0%). Furthermore, the Nail Physicians Global Assessment (PGA) improved in a

significantly greater proportion of patients in the golimumab 50 mg (60%) and golimumab 100 mg (63%) groups compared to the placebo group (18%). Median percent change from baseline in dactylitis and enthesitis tenderness score at week 24 was significantly greater for both golimumab 50 and 100 mg (100% for dactylitis; 60% and 67%, respectively, for enthesitis tenderness) versus placebo (42% for dactylitis; 12% for enthesitis tenderness) (27).

Data from the GO-REVEAL study have also enabled the investigation of the effect of golimumab treatment on pneumococcal vaccine responses in active psoriatic arthritis. In 87% of patients from this study who were receiving the pneumococcal vaccine, there was no significant difference between the golimumab (n = 249) and placebo (n = 92) groups in the proportion of patients who responded to the pneumococcal vaccine. However, the data do suggest that fewer patients receiving MTX at baseline across both active treatment groups were classified as responders to pneumococcal vaccination (28).

Sera collected at weeks 0, 4 and 14 from a subset of patients (n = 100) in the GO-REVEAL study enabled the establishment of associations between changes in serum marker levels and clinical efficacy. In the golimumab-treated patients, levels of acute-phase (CRP, IL-6, serum amyloid P, haptoglobin), inflammatory (vascular endothelial growth factor [VEGF], TNF-α, intercellular adhesion molecule 1 [ICAM-1], matrix metalloproteinase MMP-3, TNF receptor 2 [TNF-R2], RAGE-binding protein, IL-16, IL-18, IL-1Rα, IL-8, monocyte chemoattractant protein 1 [MCP-1] and macrophage inflammatory protein [MIP-1β]) and other proteins (α_1-antitrypsin, myeloperoxidase, thyroxin-binding globulin) were significantly decreased as early as week 4 and at week 14 compared with placebo-treated patients (29).

Ankylosing spondylitis

Data from the GO-RAISE study (Golimumab - A Randomized Study in Ankylosing Spondylitis Subjects of a Novel Anti-TNF mAB Injection [SC] Given Every Four Weeks) demonstrated that golimumab was effective and well tolerated in a large cohort of patients with ankylosing spondylitis during a 24-week period. S.c. injections of golimumab 50 mg (n = 138) or 100 mg (n = 140) or placebo (n = 78) every 4 weeks were shown to provide 40% improvement in the Ankylosing Spondylitis Assessment Study (ASAS) criteria at week 24 in 43.5%, 54.3% and 15.4% of patients, respectively, with a significantly higher ASAS 20 responder rate (59.4%, 60.0% and 21.8%, respectively). Patients receiving golimumab also showed significant improvements in the physical and mental component summary scores of the Short Form (SF)-36 Health Survey, the Jenkins Sleep Evaluation Questionnaire score, the Bath Ankylosing Spondylitis Disease Activity (BASDAI) score and the Bath Ankylosing Spondylitis Functional Index (BASFI) score, but not the Bath Ankylosing Spondylitis Metrology Index (BASMI) score. Up to week 24, 85.6% of golimumab-treated patients and 76.6% of patients in the placebo group reported at least one adverse event (AE), and 5.4% and 6.5% of patients, respectively, had at least one SAE. abnormal liver enzyme values (≥ 100% increase from baseline and a value of > 150 IU/L) were recorded in eight golimumab-treated patients and one placebo-treated patient; these elevations were transient in both groups (30-39).

Improvements in indices to detect improvement in enthesitis, a primary feature of ankylosing spondylitis, have also been shown in the GO-RAISE study. Statistically significant improvements were noted for 50- and 100-mg monthly regimens according to the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and University of California San Francisco (UCSF) indices (40).

Sera collected at weeks 0, 4 and 14 from a subset of patients (n = 100) in the GO-RAISE study enabled the establishment of associations between changes in serum marker levels and clinical efficacy. In the golimumab-treated patients, levels of acute-phase (CRP, IL-6, serum amyloid P, complement 3, ferritin and haptoglobin), inflammatory (VEGF, TNF-α, ICAM-1, MMP-3 and TNF-R2), lipid-related (apolipoprotein A1) and other (sex hormone-binding globulin [SHBG]) markers were shown to be significantly decreased as early as week 4 and week 14 compared with placebo-treated patients. Furthermore, additional analysis of baseline levels of select acute-phase (IL-6, leptin, haptoglobin and insulin), lipid-related (apolipoprotein C3) and inflammatory (ENA-78) markers indicated significant associations with specific clinical endpoints (ASAS 20, BASDAI and BASFI) at week 14 when golimumab treatment groups were combined. Interestingly, significant increases in bone formation markers such as osteocalcin and aminoterminal propeptide of type I collagen (PINP), and significant decreases in the bone degradation marker deoxypyridinoline as early as week 4 were observed in those treated with golimumab versus placebo (41).

Rheumatoid arthritis

A randomized, double-blind, placebo-controlled, dose-ranging study investigated the efficacy, safety and pharmacology of s.c. golimumab (50 or 100 mg given every 2 or 4 weeks) in patients with active rheumatoid arthritis despite previous treatment with MTX (N = 172) over a period of 48 weeks. A significantly greater proportion of patients receiving golimumab 100 mg plus MTX every 2 weeks achieved an ACR20 response at week 16 (79.4%) compared with those receiving placebo plus MTX (37%). No significant differences were seen versus placebo for other treatment arms. Up to week 20 (after which patients receiving placebo were switched to active infliximab therapy), at this golimumab dose regimen (n = 35), ≥ 1 AE was reported in 88.6% of patients versus 85.3% of patients receiving placebo + MTX (n = 34), with ≥ 1 serious AEs (SAEs recorded in 8.6% and 5.9%, respectively). The most common clinically relevant SAEs through week 52 in golimumab-treated patients were pneumonia (3 patients), lung cancer (unrelated, 1 patient), cardiac tamponade (1 patient) and cardiac failure (1 patient) (42-47).

Sera collected at weeks 0, 4 and 14 from 164 adults involved in the study described above (with rheumatoid arthritis of at least 3 months' duration and active despite MTX therapy) enabled the identification of molecular changes associated with clinical efficacy. Treatment with golimumab plus MTX resulted in a rapid (week 4) and prolonged (up to week 16), significant median decrease from baseline in CRP, serum amyloid A, IL-6, IL-8, E-selectin, ICAM-1, MMP-1 and MMP-3 compared with placebo plus MTX. There was further evidence for associations between biomarker plasticity and improvements in response parameters, such as tender joint count, swollen joint count and ACR50 (48, 49).

In the GO-FORWARD (GOlimumab FOR subjects With Active RA Despite MTX) study, golimumab at doses of 50 and 100 mg was studied in patients whose disease was active despite ongoing treat-

ment with MTX (N = 444). At week 14, a significantly greater proportion of patients on golimumab 50 mg (55%) or 100 mg (56%) plus MTX achieved ACR20 compared with placebo plus MTX (33%). Improvements in the Health Assessment Questionnaire (HAQ) quality-of-life scores were also evident at 24 weeks, 68% of patients in the 50-mg group and 72% in the 100-mg group experiencing clinically relevant improvements in physical function compared with 39% in the placebo plus MTX group (50).

A multicenter, randomized, double-blind study, placebo-controlled trial known as GO-AFTER (GOlimumab After Former anti-TNF Therapy Evaluated in RA) evaluated the efficacy and safety of golimumab 50 or 100 mg given every 4 weeks in patients with moderate to severe active rheumatoid arthritis who had been previously treated with anti-TNF-α agents. Data from 461 pts (50 mg, n = 153; 100 mg, n = 153; placebo, n = 155) indicated that, compared to placebo, at weeks 14 and 24 patients receiving active treatment showed significant improvements in ACR20, ACR50 and the Disease Activity Score (DAS), including the 28-joint count (DAS28), along with HAQ quality-of-life scores (assessing eight functional areas —dressing, rising, eating, walking, hygiene, reaching, gripping and other activities of daily living). Improvements in disease activity and physical function were sustained for at least 6 months. Among 58% of patients whose prior anti-TNF-α therapy had been discontinued due to lack of efficacy, significantly more patients (36% on 50 mg and 43% on 100 mg) achieved the primary endpoint (ACR20) compared with placebo (18%). This study also demonstrated that golimumab is well tolerated up to week 24, with ≥ 1 AE reported in 72.3%, 66.4% and 78.3% of patients, respectively, receiving placebo, golimumab 50 mg and 100 mg. SAEs occurred in 9.7%, 7.2% and 4.6%, respectively (51).

The efficacy of golimumab 50 mg s.c. given every 4 weeks alone or in combination with MTX versus MTX alone was investigated in a multicenter, double-blind, placebo-controlled study in MTX-naïve patients (N = 637) with active rheumatoid arthritis. Data from this study suggested that golimumab 50 mg plus MTX achieved a statistically significantly greater response in terms of multiple signs and symptoms associated with rheumatoid arthritis versus MTX alone for a period of 24 weeks (52).

Asthma

A randomized 1-year clinical study in 144 Caucasian severe asthmatics identified that genetic variations in the *TNFR* genes are related to the therapeutic response to golimumab (53).

SOURCES

Centocor Ortho Biotech (US); licensed to Schering-Plough for marketing outside the U.S., except Japan, Indonesia and Taiwan, where it will be marketed by Mitsubishi Tanabe Pharma and Janssen, and Hong Kong and China, where it will be marketed by Janssen (Johnson & Johnson).

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