

EXPERT
REVIEWSIntravenous golimumab in
rheumatoid arthritis*Expert Rev. Clin. Immunol.* Early online, 1–8 (2014)Marc D Cohen*¹ and
Edward C Keystone^{2,3}¹Mayo Clinic, 668 Humboldt St, Denver,
CO 80218, USA²University of Toronto, Toronto, ON,
Canada³Mount Sinai Hospital, The Joseph and
Wolf Lebovic Building, 2nd Fl, Room
2-006, Box 4, 60 Murray St, Toronto,
ON M5T 3L9, Canada*Author for correspondence:
mcohen@rheumdoc.net

Intravenous golimumab in a dosage of 2 mg/kg, initially given every 4 weeks but then every 8 weeks, in addition to methotrexate, is effective in the treatment of patients with rheumatoid arthritis. This weight-based infusion is administered over thirty minutes with an acceptable safety profile. Since it is a relatively new formulation, more time will be required to assess its specific role in the rheumatologists' armamentarium and to appreciate more fully its long-term safety.

KEYWORDS: anti-TNF- α antibodies • golimumab • rheumatoid arthritis treatment • safety of TNF- α inhibition • TNF- α inhibition

Overview of the market

In the past 15 years, the treatment of rheumatoid arthritis (RA) has dramatically changed, at least in part due to the emergence of biologic agents. The TNF- α inhibitors represent a class of biologics, which have been established as effective agents in RA, helping control disease activity, limiting radiographic progression and preserving function. Golimumab is currently one of five such TNF- α inhibitors. As an iv. preparation it has demonstrated similar benefits with regards to efficacy and radiographic inhibition, and its safety profile is also similarly reasonable. The iv. (iv.) form of golimumab is the only fully humanized iv. formulation available, and it is safely administered over a relatively short timeframe of 30 min. This represents a niche among the available TNF- α inhibitors, but only time will tell if usage by rheumatologists will reflect the distinctness of this product.

There are now multiple biologic agents with different modes of action available for the treatment of RA, and their efficacy and safety has now been reasonably well-defined. Multiple alternative products directed at a wide variety of immunologic targets thought to be involved in the pathophysiology of RA are also under development, and some examples include monoclonal antibodies directed at IL-6, agents that block JAK kinases and compounds that interfere with TH17 cell signaling. Not all RA patients respond to the currently available treatments, and there still are clearly unmet needs. Specific biomarkers to

measure RA disease activity and to predict response to treatments continue to be the object of much research, and more effective, safe and affordable targeted treatments will hopefully emerge in the future. Until then, the currently available biologics, like iv. golimumab, offer important, substantially effective treatment options for RA.

Type of drug

Golimumab is a fully human monoclonal antibody to TNF- α , which binds to soluble and transmembrane TNF- α preventing binding to TNF- α receptors and thereby inhibiting TNF- α activity. It is similar to infliximab except that it is fully human with the constant region sequences identical to infliximab [1]. Its molecular weight is also identical to infliximab at 149 kDa. The fully human structure of golimumab potentially allows a different response compared with the chimeric structure of infliximab.

Dosing

Golimumab is given in the dose of 50 mg per month as a subcutaneous injection. As an iv. preparation, the recommended dose is 2 mg/kg per 8 weeks.

Pharmacokinetics

The pharmacokinetic characteristics of golimumab were evaluated after a single iv. administration in patients with RA [2] and a single subcutaneous administration in healthy subjects [3]. In the former study, the C_{max} increased in a dose-proportional manner over the dose range 0.1–10 mg/kg. Mean clearance

was estimated to be 4.9–6.7 ml/day/kg, and the half-life ranged from 8 to 20 days. In the latter subcutaneous study, a single golimumab administration of 100 mg was absorbed slowly into the blood with a median T_{max} of 4 days, and a median half-life of 10.9 days.

In an open-label Phase I study [4], 49 patients with RA received subcutaneous golimumab 100 mg ($n = 33$) every 4 weeks through week 20 or iv. golimumab 2 mg/kg ($n = 16$) at weeks 0 and 12. After the subcutaneous dose, the serum golimumab concentration achieved steady state by approximately 12 weeks with mean trough concentrations of 1.15–1.24 $\mu\text{g/ml}$. After the final 30-min iv. infusion, the mean golimumab clearance was 7.5 ml/day/kg. The mean terminal half-life after either administration was approximately 13 days. The median T_{max} value was in the range of 3–4 days regardless of concomitant methotrexate (MTX) use. The drug was well tolerated in this study. There were no apparent clinically relevant differences observed in the pharmacokinetic characteristics of golimumab between the patients with RA in this study and those reported previously in healthy subjects.

Mechanism of action

Given the similarities of the product to infliximab, golimumab shares the same mechanism of action [1]. By inhibiting TNF- α , it interferes with the proinflammatory cascade. This results in inhibition of myriad pathways, including cellular migration, infiltration and activation, cytokine and chemokine production, matrix metalloproteinase production, angiogenesis, osteoclast maturation and bony damage.

Also like infliximab, golimumab has the potential to lyse cells with transmembrane TNF- α on their surface and to participate in antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Golimumab binds to soluble and transmembrane TNF- α with great avidity and affinity, resulting in TNF- α neutralization. The clinical relevance of these properties has not yet been determined.

Initial clinical studies of subcutaneous golimumab in RA

A Phase II dose-ranging study of golimumab was conducted in RA patients with an incomplete response to MTX [5]. Although this study confirmed the efficacy of golimumab compared with placebo in this patient group, study design issues may have precluded detection of differences between the different treatment arms of golimumab 50 mg every 2 or 4 weeks and 100 mg every 2 or 4 weeks. Nonetheless, the treatment arms of golimumab 50 and 100 mg every 4 weeks were selected for further study.

The Phase III GO-BEFORE trial evaluated the efficacy of golimumab as monotherapy or in combination with MTX in RA patients who were MTX-naïve [6]. The primary end point selected was the percentage of patients achieving an American College of Rheumatology improvement criteria (ACR50) response rate at 24 weeks and changes in radiographic scores at 52 weeks. By intent-to-treat analysis, the primary end point of a greater proportion of patients in the golimumab (50 and

100 mg) plus MTX achieving an ACR50 response rate compared with MTX alone was not achieved. However, golimumab plus MTX inhibited radiographic progression more than MTX alone [7]. Additionally, most of the preselected secondary outcome measures were achieved.

The Phase III GO-FORWARD trial assessed the efficacy of golimumab in RA patients with an incomplete response to MTX [8]. Both 50 and 100 mg golimumab every 4 weeks plus MTX groups achieved an ACR20 (and ACR50/70, DAS28 and DAS28-remission) response rate, which was statistically superior to placebo plus MTX. Radiographic progression in this study was minimal in all treatment arms, and the effect of golimumab on radiographic progression was not obviously superior to placebo.

The Phase III GO-AFTER trial assessed the efficacy of golimumab in RA patients who were incomplete responders to other TNF- α inhibitors [9]. In patients who had discontinued their prior TNF- α inhibitor for lack of efficacy, 35.7 and 42.7% of patients in the 50 and 100 mg every 4 week golimumab groups achieved an ACR20 response rate versus 17.7% in the placebo group at week 14, $p < 0.001$. Golimumab also resulted in statistically significant improvements in DAS28 response changes and the achievement of DAS28-remission. This was the first double-blind, placebo-controlled, prospective trial to demonstrate the efficacy of a TNF- α inhibitor in patients with RA and a prior incomplete response to other TNF- α inhibitors.

In psoriatic arthritis, the Phase III GO-REVEAL study demonstrated the significant efficacy of golimumab in the treatment of psoriatic arthritis, including the joint, skin, nail, dactylitis and enthesitis components [10].

The Phase III GO-RAISE trial established the efficacy of golimumab in ankylosing spondylitis [11]. The clinical benefit, improvement in physical function and improved sleep were significant and sustained.

Clinical trials of iv. golimumab in RA (TABLE 1)

First Phase III study

iv. golimumab was evaluated in a Phase III randomized, double-blind, placebo-controlled trial by Kremer *et al.* [12]. In this study, 643 RA patients who were incomplete responders to MTX at a dosage of 15–25 mg/week for 4 weeks or longer were randomized to receive iv. infusions of placebo plus MTX or iv. infusions of golimumab at a dose of 2 or 4 mg/kg, with or without MTX, every 12 weeks through week 48. Patients with less than a 20% improvement in swollen and tender joint counts were eligible to enter early escape and received additional active treatment at week 16 or had their dosage increased at week 24. The primary end point was the proportion of patients achieving a 50% response according to the ACR50 at week 14 (TABLE 1).

At week 14, an ACR50 response was observed in 21% of the patients treated with golimumab plus MTX ($n = 129$) compared with 13% of the patients treated with placebo plus MTX ($n = 257$) ($p = 0.051$), and the primary study end point

Table 1. The Phase III clinical trials of intravenous golimumab in rheumatoid arthritis.

Study (year)	Trial info	Golimumab	Dosing end points (response met)	Ref.
Kremer <i>et al.</i> (2010)	643 RA pts, 5 groups	2 or 4 mg/kg or placebo q12 wks, with or without MTX	Primary: ACR50 response at wk 14 (not met) Secondary: ACR50 response at wk 24 (met), HSF-36 at wk 24 (met), no differences in mono- vs combination	[12]
Weinblatt <i>et al.</i> (2013)	GO-FURTHER 592 RA pts, 2 groups	2 mg/kg or placebo 0, 4 wks, then q8 wks with MTX	Primary: ACR20 response at wk 14 (met) Secondary: ACR20 response at wk 2; ACR20/50/70 response, DAS28-CRP, CDAI, SDAI, HAQ at wk 24	[13]
Weinblatt <i>et al.</i> (2013)	GO-FURTHER	Same as above	Primary: maintenance of ACR20 response to wk 52 and T vdH-S at wk 52. Secondary: maintenance of ACR50/70 response, DAS28 CRP, CDAI, HAQ at wk 52; E/JSN scores at wk 52	[14]

ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; MTX: Methotrexate; pts: Patients; SDAI: Simplified Disease Activity Index; wk: Week.

was not met. By week 24, however, significantly more patients treated with golimumab plus MTX had achieved an ACR50 response compared with placebo, 22 versus 9% ($p = 0.002$). There were no differences in the proportion of patients achieving an ACR50 response between the group receiving golimumab monotherapy and the group receiving placebo plus MTX at either week 14 (16 vs 13%) or week 24 (10 vs 9%). At week 48, the proportions of patients achieving ACR50 responses were highest in the patients who had received golimumab 4 mg/kg plus MTX.

A secondary analysis using the median change from baseline in the physical component summary score of the Medical Outcomes Study 36-item Short-Form health survey (SF-36) at week 14 demonstrated significant changes among those patients receiving golimumab plus MTX compared with those receiving placebo plus MTX, 6.1 versus 3.4 ($p = 0.005$). Changes were not different in the golimumab monotherapy groups and the placebo plus MTX group. At week 48, patients in the 2 and 4 mg/kg golimumab plus MTX groups had median improvements of 8.4 and 8.8, respectively.

Antibodies to golimumab were detected in 5% of golimumab-treated patients through week 24. A higher proportion of patients receiving golimumab monotherapy demonstrated antibodies to golimumab compared with those receiving golimumab plus MTX (9 vs 3%), and only one patient in the 4 mg/kg golimumab plus MTX group exhibited antibodies to golimumab (0.8%).

None of the antibody-positive patients had infusion reactions through week 24. The proportion of patients achieving an ACR50 response was higher in the patients with negative antibody status compared with those with positive antibody status.

Serum golimumab concentrations were approximately proportional to the dose of golimumab. After the first infusion, the median peak concentrations were 35 and 70 $\mu\text{g/ml}$ for the 2 and 4 mg/kg doses, respectively, regardless of MTX treatment. The median trough serum golimumab concentrations at week 12 were below the limit of quantification of 0.2 $\mu\text{g/ml}$ for all of the golimumab treatment groups, clearly lower than anticipated. This low drug concentration was suggested as the

likely reason for the lack of a robust and sustained ACR response when the efficacy was assessed at earlier time points through week 24. The median serum golimumab concentrations at week 8 were 0.23 and 0.53 $\mu\text{g/ml}$ for the groups receiving 2 and 4 mg/kg golimumab plus MTX, respectively. This led the authors to conclude that shortening the dosage interval to every 8 weeks might provide improved drug exposure and thus an improved ACR response, particularly for the initial treatment with golimumab.

The majority of the golimumab infusions were administered within 25–35 min at all time points. There were no severe infusion reactions, and the total number of infusion reactions were relatively low (2.2%). There were no reports of anaphylaxis or serum sickness.

The rates of total adverse events (AEs) through the placebo-controlled phase of the trial were similar between the golimumab-treated patients and the placebo plus MTX-treated patients, 66 versus 67%. The most commonly reported AEs were infections, 48 versus 41%. There was no obvious relationship between the overall AE rate and golimumab dose. Higher proportions of all golimumab-treated patients than placebo plus MTX-treated patients experienced serious AEs, 4 versus 2%.

The rate of serious infections in the golimumab-treated patients was twice that observed in the patients who received placebo plus MTX, although the overall rate was low (10 vs 5%). There were two cases of TB between weeks 24 and 48 in patients who had negative TB screening prior to infusion. Although there were no deaths during the initial 24 weeks of the study, there were 5 deaths reported after week 24 distributed between the active arms of the trial, 3 from myocardial infarction, 1 from septic shock and 1 from unknown causes. Malignancies were reported in two patients during the first 24 weeks of the trial, both in the placebo plus MTX patient group. From week 24 through 48, there were eight malignancies of varying types with at least one in all treatment groups. The authors concluded that golimumab treatment does not appear to be associated with the onset of malignancies.

Taken together, the reported AEs associated with iv. administered golimumab appear similar to those associated with subcutaneously administered golimumab as well as other TNF- α inhibitors, whether in combination with MTX or without concomitant MTX.

Although the study did not achieve its primary end point, the authors concluded that treatment with iv. administered golimumab plus MTX was beneficial to a group of RA patients with a previous incomplete response to MTX by reducing signs and symptoms and improving physical function, particularly beyond the 14-week primary end point. The authors also remarked that the dosing strategy of every 12 weeks appeared inadequate. They suggested further study of treatment with the 2 mg/kg golimumab dose, but using a different dosing strategy. Subsequently, such a study was designed, and the initial results published.

The pivotal GO-FURTHER study

The conclusions from the original Phase III trial may have been utilized in a subsequent double-blind, placebo-controlled Phase III trial, the so-called GO-FURTHER trial [13]. This trial included patients with more active RA, with greater disease activity as per baseline DAS28 scores, higher median C-reactive protein levels and higher Health Assessment Questionnaire (HAQ) scores, compared with the first trial. Additionally, the patients received more frequent golimumab infusions. In this study, 592 RA patients with active disease despite MTX 15–25 mg/week for greater than 4 weeks were randomized 2:1 to receive ongoing weekly MTX and iv. golimumab 2 mg/kg or placebo infusions at weeks 0 and 4 and every 8 weeks. Placebo patients with less than 10% improvement in combined swollen and tender joint counts at week 16 could early escape to active golimumab treatment. The primary end point was the ACR20 response at week 14. Analyses employed non-responder imputation and last observation carried forward.

The results demonstrated an ACR20 response rate of 58.5% (231/395) in the golimumab plus MTX patients versus 24.9% (49/197) ($p < 0.001$) in the placebo plus MTX patients at week 14, achieving the primary end point. A significant difference in ACR20 response was observed as early as week 2, 33.2% (131/395) versus 11.7% (23/197) ($p < 0.001$). Significant treatment group differences were consistent across other response measures, including DAS28-CRP, Clinical Disease Activity Index, Simplified Disease Activity Index and HAQ. At week 14, patients in the golimumab plus MTX group demonstrated significantly greater mean improvement in the HAQ score, 0.5 versus 0.19 ($p < 0.001$) for the placebo plus MTX patients. Nearly 70% of golimumab-treated patients achieved a clinically meaningful improvement (0.25 units) in the HAQ score by week 14. Also at week 14, a significantly greater proportion of patients in the golimumab plus MTX-treated patients demonstrated a European League Against Rheumatism moderate/good response based on DAS28-CRP versus the placebo plus MTX-treated patients, 81.3 versus 40.1% ($p < 0.001$), and 65% of the golimumab-treated patients achieved a European League Against Rheumatism response by week 2.

At week 24, the significant difference in ACR20 responses was maintained. Also, the proportion of patients in the golimumab plus MTX group achieving ACR50/70 responses were significantly greater than in the placebo plus MTX group, 34.9/17.7 versus 13.2/4.1%, respectively ($p < 0.001$ for both). The proportion of ACR50 responders increased from 29.9% at week 14 to 34.9% at week 24. Among golimumab-treated patients, the maximum improvement based on ACR criteria tended to occur at week 24. Small decreases in response rates were noted at weeks 12 and 20, the presumed timing of trough serum golimumab concentrations, compared with 4 weeks earlier, at weeks 8 and 16, respectively. At all assessment time-points from week 4, forward response rates were significantly higher with golimumab plus MTX compared with placebo plus MTX.

Antibodies to golimumab were detected in 13 (3%) of 440 golimumab-treated patients through week 24. Serum golimumab concentrations were generally lower in patients who tested positive for antibodies to golimumab.

Adverse events

During the 16-week placebo-controlled study period, AEs were higher in the golimumab plus MTX group compared with the placebo plus MTX group. Of these, AEs infection rates were 24.3 versus 20.8%, headaches and nervous system symptoms 6.8 versus 4.1%, gastrointestinal symptoms 6.6 versus 5.6%, skin symptoms 6.6 versus 3.6% and respiratory symptoms 4.6 versus 2.5%, respectively. Serious AEs (four events in three patients) demonstrated no obvious trend and there were no opportunistic infections or TB. One patient receiving placebo plus MTX died of a stroke. There was one malignancy (breast cancer) in the golimumab plus MTX group, and one (lung adenocarcinoma) in the placebo plus MTX group.

Infusion reactions were reported in 16 (3.5%) patients in the combined golimumab plus MTX groups versus 1 (0.5%) in the placebo plus MTX group. There were no differences in infusion reactions based upon whether or not patients received standard infusion reaction prophylaxis, which was discretionary. The mean infusion time was 30 min, and 86.7% of the infusions were completed within 40 min.

Mild transaminase increases ($<2 \times$ upper limit of normal) were seen in 2.1% of the golimumab plus MTX patients versus 21.6% of the placebo plus MTX patients. Two patients receiving golimumab had $>5 \times$ upper limit of normal alanine aminotransferase levels.

Taken together, the results demonstrate that iv. golimumab, at 2 mg/kg, rapidly and significantly improved the signs and symptoms of RA in MTX-incomplete responders. This regimen was well tolerated with no new safety concerns. The GO-FURTHER trial continues through 112 weeks.

Although comparisons across different studies are fraught with difficulties, the ACR response rates reported in this article were similar to those reported in the TNF- α -inhibitor trials using subcutaneous golimumab and those reported with the other TNF- α inhibitors. The rapid clinical effects were obvious and potentially important. The safety profile was not significantly different than those of other TNF- α inhibitors.

The GO-FURTHER trial at 52 weeks

The radiographic benefit and maintenance of the clinical benefit with results up to 1 year of the GO-FURTHER trial were reported in a separate publication [14]. At 52 weeks, clinical efficacy ACR20/50/70 response rates were 65.8%/38.7%/18.2% in those patients who received golimumab plus MTX for a full year. Of the golimumab-treated patients who achieved an ACR response rate at week 24, 82% (201/245) maintained this response at week 52, and of the ACR20 non-responders at week 24, 40.1% (55/137) achieved this response by week 52. Also, 88% of the golimumab-treated patients who achieved a DAS28-CRP good/moderate response at week 24 maintained this level of response up to week 52. Improvements in HAQ-DI scores achieved at week 24 were generally maintained through week 52 in the golimumab plus MTX-treated patients, with mean changes of 0.38 from baseline to week 52.

Patients who received golimumab plus MTX demonstrated significantly less radiographic progression from baseline to week 24 in total vdH-S score versus patients who received placebo plus MTX, mean change 0.03 versus 1.09 ($p < 0.001$). Larger proportions of patients who received golimumab plus MTX compared with placebo plus MTX demonstrated a change of 0 or less in total vdH-S score, 70.6 versus 57.4% ($p = 0.001$). Based on the smallest detectable change (SDC) in overall radiographic progression (SDC = 1.91), lower proportions of patients progressed in the golimumab plus MTX group compared with the placebo plus MTX group, 8.6 versus 19.3% ($p < 0.001$). In erosion alone (SDC = 1.57), progression was 3.8 versus 10.7% ($p = 0.001$) and in joint space narrowing alone (SDC = 1.19) 9.9 versus 17.3% ($p = 0.010$). Additionally, less absolute progression with golimumab plus MTX versus placebo plus MTX was observed in erosion (mean changes of -0.12 vs 0.53 ; $p < 0.001$) and joint space narrowing (0.14 vs 0.56 ; $p = 0.002$).

At week 52, patients randomized to placebo plus MTX (who received golimumab plus MTX from weeks 16 to 52 or from weeks 24 to 52) exhibited significantly more radiographic progression than those patients who received golimumab plus MTX beginning at week 0, 1.22 versus 0.13 ($p = 0.001$). From weeks 24 to 52, those patients initially randomized to golimumab plus MTX generally demonstrated minimal change in total vdH-S score, mean change 0.15. Patients initially randomized to placebo plus MTX who began golimumab plus MTX at week 16 or 24 also demonstrated limited radiographic progression between weeks 24 and 52, mean change 0.12, with progression similar to patients initially randomized to active drug. This suggests stabilization of radiographic disease within 6 months after the onset of golimumab therapy.

Golimumab serum concentration achieved steady state by week 12, with median trough concentrations of 0.27, 0.21 and 0.30 $\mu\text{g/ml}$ at weeks 12, 20 and 52, respectively. This suggests maintenance of drug exposure through week 52 with an infusion schedule of golimumab 2 mg/kg every 8 weeks.

The incidence of antibodies to golimumab was 3.0% at week 24 and 4.6% at week 52. In all of the 26 antibody-positive

patients, the antibodies were neutralizing. At week 52, ACR20 and ACR50 responses were observed in 14 (53.8%) of 26 and 5 (19.2%) of 26 patients who were antibody positive, respectively, compared with 353 (66.1%) and 203 (38%) of 534 patients who were antibody negative, respectively. These data suggest that anti-golimumab antibodies diminish the drug's clinical efficacy. There was no obvious relationship between antibodies to golimumab and the development of infusion reactions.

Safety observations through 52 weeks revealed that 64.6% of all golimumab plus MTX-treated patients reported an AE, an increase from the 52.9% AE rate reported up to week 24. The most commonly reported AEs continued to be upper respiratory tract infection, bronchitis, headache, nasopharyngitis, hypertension and urinary tract infection. Similarly, the rate of serious AEs among all golimumab plus MTX-treated patients increased from week 24 to 52, 4.1–8.6%. Serious infections again comprised the most commonly reported serious AE, occurring in 1.9% of all golimumab plus MTX-treated patients. The serious infections were described as singular events. One patient with negative TB screening was subsequently diagnosed with fatal abdominal TB. No opportunistic infections were documented through week 52, but one patient developed uncomplicated cryptococcal pneumonia after week 52.

From week 24 to 52 in the golimumab plus MTX-treated patients, there two additional malignancies reported, one case of stage 0 cervical carcinoma and one case of basal cell carcinoma. There were three serious cardiovascular events during this period, including unstable angina, atrial fibrillation and a presumed myocardial infarction, which was fatal.

The overall rate of infusion reactions was 0.7%, and the most common manifestation was skin rash, with bradycardia and palpitations and hypotension and flushing also described in patients receiving golimumab plus MTX. No infusion reaction was severe or serious and no delayed hypersensitivity or serum sickness was described.

The results of the 52-week study supported the concept that iv. administered golimumab both maintained its clinical effect and significantly inhibited radiographic progression. The safety findings reported with iv. administered golimumab seemed quite comparable to the subcutaneous golimumab findings, and this was further supported by data from an iv. to subcutaneous switch golimumab trial of patients with RA, in which AE rates adjusted for length of follow-up were generally comparable between iv. and subcutaneous adalimumab administration [14].

The radiographic results of the study appear similar to those exhibited by the other TNF- α inhibitors in previous studies. In previous studies, the percentage of patients with no radiographic progression is significant in both the active study drug group and the placebo group, and a relatively small number of patients with some radiographic progression drive any significant difference between these groups. Also, with the results often presented as mean differences in erosions and joint space narrowing, individual patients may be overrepresented in any particular change. This study similarly presents radiographic

results, and interpretation of the findings warrants careful analysis of the cumulative probability plot and which might be aided by presentation of changes by quartiles.

Additional studies

A study evaluated the maintenance of efficacy and safety with subcutaneous golimumab among patients with active RA who previously received iv. golimumab [15]. Six hundred and forty-three RA patients with an incomplete response to MTX were randomized to iv. golimumab 2 or 4 mg/kg with or without MTX every 12 weeks ($n = 514$) or iv. placebo plus MTX. Patients who completed the study through week 48 were eligible for the long-term extension study, utilizing open-label golimumab 50 mg subcutaneously every 4 weeks with or without MTX for an additional 24 weeks.

At week 48, 28% of patients who received iv. golimumab plus MTX achieved an ACR50 response versus 11% of patients receiving golimumab alone and versus 8% of patients receiving placebo plus MTX. Among the 505 patients who participated in the long-term extension part, the ACR50 response increased to 44% at both weeks 24 and 48. Infections were the most commonly observed AEs, although fairly evenly distributed among all groups. Among patients who received iv. golimumab with or without MTX, serious AEs were reported in 9 and 7% of patients, infections requiring antibiotics in 27 and 24% of patients and serious infections 4 and 2%. There was one case of TB and no opportunistic infections. There were three deaths, one in each golimumab group. There were 2 neoplasms in the placebo plus MTX group, but 17 among the golimumab groups without an obvious dominant type. Concomitant MTX use yielded lower incidences of antibodies to golimumab and injection site reactions. Pharmacokinetic studies demonstrated median trough serum levels with iv. golimumab every 12 weeks, which were below the limit of quantification ($0.2 \mu\text{g/ml}$) in three of the four golimumab treatment groups, and patients receiving 4 mg/kg plus MTX exhibited steady state trough concentrations levels of $0.2\text{--}0.3 \mu\text{g/ml}$. These low levels provide a pharmacological explanation for the observation that ACR responses induced by iv. treatment every 12 weeks were improved by subcutaneous golimumab during the long-term extension and without additional toxicity or safety concerns.

Conclusion

iv. golimumab plus MTX has been demonstrated to be efficacious in RA patients who are incomplete responders to MTX, with statistically significant improvements in clinical indices, function and radiographic inhibition. Pharmacokinetic studies suggest that 2 mg/kg initially every 4 weeks but then every 8 weeks provides adequate drug through the treatment period. The safety profile appears similar to that of subcutaneous golimumab and to other TNF- α inhibitors with no obvious distinct signals. The follow-up period for iv. golimumab in RA is short since it has only recently been approved, and further study will be required to appreciate fully its safety profile. Specifically, the iv. route of golimumab administration has not yet been included

in any of the large ongoing registries following patients with RA treated with biologics, and several years will be required before accurate, longer-term comparisons to other TNF- α inhibitors will be available from these sources.

iv., weight-based golimumab plus MTX given every 8 weeks in a 30-min infusion appears to be a valuable addition to the rheumatologists' armamentarium for the treatment of certain patients with RA. It provides more flexibility with regards to golimumab administration, and this may be particularly significant in patients with high BMIs, where higher doses of drug might be important [16]. Further studies will be required to define its use more critically and to appreciate its long-term safety profile.

Expert commentary

Patients with RA who demonstrate an incomplete response to traditional disease-modifying agents such as MTX often require more aggressive treatments with biologic agents. The specific targets toward which such treatments are directed have been better defined over the last several years and now include the concept of remission. Additionally, the number of biologic agents for use in RA has expanded. The TNF- α inhibitors have been effective drugs, often in combination with MTX, in patients responding insufficiently to traditional agents, with a wealth of experience reported establishing their efficacy and defining safety concerns. Golimumab is a fully humanized monoclonal antibody to TNF- α , and its use in the subcutaneous form has been reported in RA and other types of inflammatory arthritis. A weight-based iv. infused form of this agent has recently become available, and its efficacy in combination and relative safety in the treatment of RA has been reported. Studies have demonstrated that it can be infused over 30 min, and after a loading dose of every 4 weeks, it may be used every 8 weeks. Because it is weight based, because its infusion duration is relatively short and because infusions are required only every 8 weeks, iv. golimumab has certain advantages compared with other biologic agents in the treatment of RA. Exactly where iv. golimumab will be placed in the armamentarium of practicing rheumatologists will evolve over the next several years, as more information is acquired regarding its long-term efficacy and safety profiles.

Five-year view

The TNF- α inhibitors have an established place as effective agents in patients with an insufficient response to traditional therapeutic agents such as MTX. iv. golimumab has certain advantages among the other clinically available TNF- α inhibitors and among the other biologic agents available for the treatment of RA: a weight-based formulation, a relatively short infusion time and 8 weeks between ongoing infusions. Whether or not these advantages will be recognized by clinicians, and lead to the regular use of golimumab remains to be seen. An increasing number of biologic agents with alternative mechanism of action will become available in the next several years, so the place of TNF- α inhibitors like iv. golimumab will continue to undergo scrutiny and will undoubtedly change. RA treatments should

evolve and hopefully improve over the next 5 years as specific treatments are more tailored to individual RA patients.

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Key issues

- intravenous (iv.) golimumab plus methotrexate (MTX) is efficacious in the treatment of rheumatoid arthritis (RA) patients.
- A dose of 2 mg/kg of golimumab infused initially every 4 weeks but then every 8 weeks plus MTX is an effective regimen.
- The safety profile of iv. golimumab plus MTX is similar to the other TNF- α inhibitors.
- iv. golimumab plus MTX rapidly improved sign and symptoms in patients with active RA despite MTX.
- iv. golimumab plus MTX demonstrated sustained efficacy up to 1 year of study.
- Those RA patients treated with golimumab plus MTX demonstrated less radiographic progression.
- The most common adverse events reported in RA patients receiving golimumab plus MTX were non-serious infections.
- The exact place of iv. golimumab among the other available TNF- α inhibitors and among other available biologics remains to be determined.

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 - This study established the currently used dose and frequency of administration of intravenous golimumab plus methotrexate as well as its clinical efficacy and safety profile.

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- This study established the long-term efficacy of intravenous golimumab plus

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