Review

Golimumab, the newest TNF-α blocker, comes of age

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Received on July 14, 2014; accepted in revised form on October 3, 2014.

Clin Exp Rheumatol 2015; 33: 570-577.

Key words: golimumab, tumour necrosis factor-α, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, treatment

Competing interests: none declared.

ABSTRACT

Golimumab, a fully human monoclonal antibody against tumour necrosis factor-α (TNF-α) is one of the newest biologics that has become available for the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Following the initial randomised double-blind placebo-controlled clinical trials, which demonstrated the efficacy and safety of the drug in the context of a limited patient sample and a relatively short time frame, golimumab has been the focus of continuous investigation through the extensions of the above-mentioned trials, new clinical trials and registries of biologic drug use in daily clinical practice. The review of this data and their inclusion in meta-analyses and indirect comparisons across TNF-α blockers suggest that golimumab possesses similar properties regarding efficacy and safety as the older monoclonal anti-TNF-α antibodies. The novelty of golimumab is perhaps its dosing regimen, i.e. subcutaneous self-administration once monthly, which allows for the least disturbance in the life of patients.

Introduction

In general, the profile of a newly-released medicinal product is determined by the generic characteristics of the pharmaceutical category it falls into, as well as the data from clinical trials that have provided support to its licensing. Thenceforth, the drug profile is constantly updated on the basis of new information deriving from additional clinical trials and long-term extensions of the initial ones, registries, clinical experience and the spontaneous reports of adverse events.

After almost a decade of experience with the tumour necrosis factor-α (TNF-α) blockers in rheumatology, a new member has been added to this class of biologic agents: golimumab. In adult rheumatology golimumab has been tried and ultimately approved across all three indications of TNF-α inhibitors, rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Golimumab has been available in the market for more than 4 years, and during that time, plenty of new information has been collected through clinical trials, long-term observations and registries. In the following sections, this data on the clinical use of golimumab will be reviewed with the aim to help update the profile of this biologic drug and point out the potential peculiarities with respect to the other members of this class of drugs.

Pharmaceutical properties

Golimumab is an $IgG_1\kappa$ monoclonal antibody against TNF-α. As it has been produced in human IgG sequence-transgenic mice that have been immunised against human TNF-α, the resulting antibody consists completely of human sequences. Its affinity with TNF-α is comparable to that of etanercept, greater than infliximab and significantly greater than adalimumab. *In vitro* equivalent biological effects may be elicited with golimumab concentrations nearly 3 times lower than infliximab and adalimumab (1).

In the European Union golimumab in combination with methotrexate (MTX) has been approved for the treatment of adults with moderately to severely active RA after failure of non-biologic disease-modifying anti-rheumatic drugs (nbDMARDs), as well as MTX-naïve adults with severe active and progressive RA. It is also indicated with or without concomitant MTX for adult patients with active and progressive PsA who have not previously had an adequate response to nbDMARDs and for adults with severe active AS after failure of non-steroidal anti-inflammatory drugs (NSAIDs). The drug is administered once monthly with a subcutaneous injection of a 50 mg dose.

After subcutaneous administration, its bioavailability is about 51% and the serum steady state concentration is attained after 12 weeks. The terminal half-life is 12±3 days, while in subjects on MTX the apparent clearance is reduced by 36% (2-3).

Data on long-term efficacy

Rheumatoid arthritis

In the context of randomised double-blind placebo-controlled clinical trials, golimumab has been tried in three categories of RA patients: MTX-naïve patients (GO-BEFORE), patients with active RA despite MTX (GO-FORWARD) and patients with active RA with previous failure to at least one TNF-α inhibitor (GO-AFTER). All three trials had similar designs. In GO-BEFORE and GO-FORWARD patients were randomised into four groups (golimumab 50 mg/4 weeks plus MTX, golimumab 100 mg/4 weeks plus MTX, golimumab 100 mg/4 weeks plus placebo MTX, MTX plus placebo golimumab). In GO-AFTER, MTX or another nbDMARD were not mandatory per protocol and thus patients were randomised into 3 groups (golimumab 50 mg/4 weeks, golimumab 100 mg/4 weeks or placebo golimumab).

Focusing on the primary endpoints and the approved golimumab dosage for RA, the outcomes of the double-blind phases were briefly as follows: in GO-BEFORE, 40.3% of patients receiving golimumab 50 mg plus MTX achieved a 50% American College of Rheumatology (ACR) response at week 24 as opposed to 29.4% of patients on MTX monotherapy (p=0.042) (4). At week 52, the mean van der Heijde-Sharp Score (vdHSS) increased by 0.74±5.23 in the golimumab 50 mg plus MTX group and by 1.37±4.56 in the MTX monotherapy group (p=0.015) (5). In GO-FORWARD, 55.1% of patients on golimumab 50 mg plus MTX achieved an ACR 20 response at week 14 as compared to 33.1% of patients on MTX only (p=0.001). At week 24, the median change of the Health Assessment Questionnaire (HAQ) was -0.38 for the golimumab 50 mg plus MTX group and -0.13 for the MTX-only group (p≤0.001) (6). Finally, in GO-AFTER 35% and 18% of patients who had received golimumab 50 mg or placebo respectively achieved an ACR 20 response at week 14 (p=0.0006), while at week 24 the respective percentages were 34% and 17% (p=0.0005) (7).

Upon completion of the double-blind phase (at 52 weeks for GO-BEFORE and GO-FORWARD and at 24 weeks for GO-AFTER), patients were allowed to continue in an open-label extension of the trials with an overall length of up to five years, during which they would receive golimumab 50 or 100 mg/4 weeks. Throughout the long-term extensions the doses of the concomitant glucocorticoids and MTX could be modified and patients were also permitted a single switch between golimumab dosages (100 mg and 50 mg monthly).

In GO-BEFORE, of the 634 patients who had initially received treatment, 419 (66.1%) remained on golimumab until week 252, while 215 withdrew (of whom 111 due to adverse events and 23 for loss of efficacy). As shown in Figure 1A, golimumab maintained adequate clinical efficacy in those patients who continued to receive it through 5 years. In terms of radiographic progression, the mean change from baseline of the vdHSS at week 104 was -0.03 in the group initially randomised to golimumab 50 mg plus MTX, 0.94 in patients who had initially been randomised to MTX monotherapy (and from week 52 on received additional golimumab) and 2.54 in those who had received golimumab 100 mg in monotherapy all since baseline. At 5 years the respective changes were 0.7, 2.3 and 1.8 showing that the initial combination therapy with golimumab plus MTX conferred greater structural benefit than initial monotherapy with MTX or golimumab (8-9), a finding that is, besides, in line with similar finding from studies with adalimumab (10-11).

In GO-FORWARD, of the 444 patients randomised at baseline, 313 (70.5%) stayed on treatment until week 252, while 131 withdrew (of whom 64 due to adverse events and 25 for loss of efficacy). As shown in Figure 1B, the drug retained stable effectiveness also in this group of patients with previous failure to MTX throughout 5 years of continuous treatment. As regards structural damage progression, although during the double-blind phase the initial combination treatment with golimumab plus MTX or initial golimumab 100 mg monotherapy had not been proven better than initial MTX monotherapy, both at 2 and 5 years patients in the initial combination therapy with golimumab 50 mg plus MTX did numerically better in terms of vdHSS than the other two groups (5, 12-14).

Finally, in GO-AFTER, out of initially 459 treated patients, 183 (39.9%) continued treatment until week 252, while 276 withdrew (of whom 86 due to adverse events and 107 for loss of efficacy). The efficacy of golimumab in this group of patient with previous failure to at least one TNFα inhibitor was, in general, lower and the percentages of patients who stopped treatment, mainly due to inefficacy, higher than in the previous couple of trials (Fig. 1C). The response to golimumab during the double-blind phase was better in patients who had previously received one rather than two or three TNF-α blockers, particularly if that agent had been etanercept or infliximab (15). However, it seems that the percentage of patients who achieve moderate-to-high clinical response since the third month of treatment remains relatively stable throughout the 5-year open-label extension (16-17).

In addition to the above placebo-controlled clinical trials, recently the results of the GO-MORE trial have been published. This study, which had a design closer to everyday clinical practice than the previous more "strict" protocols, was a large open-label trial of golimumab in patients with active RA despite nbDMARDs and/or glucocorticoids who were TNF-α blocker-naïve. Patients were added golimumab 50 mg monthly on top of the already received anti-rheumatic treatment and the efficacy and safety were assessed at 6 months. Overall 3280 patients were enrolled, of whom 51.4% had been receiving MTX monotherapy, 27.6% MTX in combination with antimalarials and/or sulphasalazine or leflunomide, 9.3% leflunomide monotherapy and 11.7% other nbDMARD combinations.

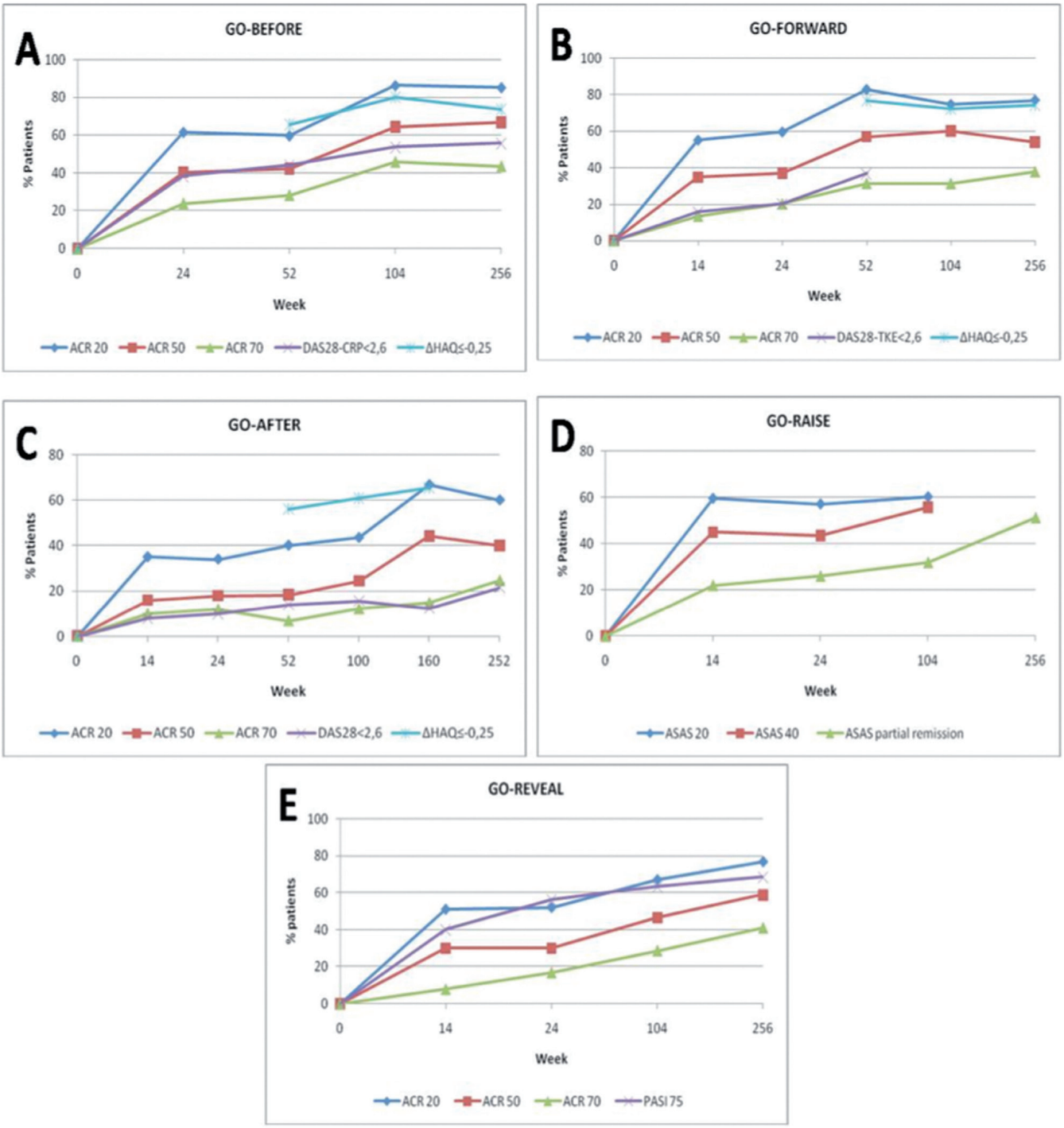

Fig. 1. Long-term efficacy of golimumab for up to 252 weeks **A.** During the extension of the GO-BEFORE trial in rheumatoid arthritis patients who at baseline had been randomised to golimumab 50 mg plus MTX. **B.** During the extension of the GO-FORWARD trial in rheumatoid arthritis patients who at baseline had been randomised to golimumab 50 mg plus MTX. **C.** During the extension of the GO-AFTER trial in rheumatoid arthritis patients who at baseline had been randomised to golimumab 50 mg. **D.** During the extension of the GO-RAISE trial in ankylosing spondylitis patients who at baseline had been randomised to golimumab 50 mg. **E.** During the extension of the GO-REVEAL trial in psoriatic arthritis patients who at baseline had been randomised to golimumab 50 mg. ACR: American College of Rheumatology; DAS28: Disease Activity Score-28 joints; ΔHAQ: Difference in Health Assessment Questionnaire; ASAS: Assessment of SpondyloArthritis international Society; PASI: Psoriasis Area and Severity Index.

At 6 months, moderate European League Against Rheumatism (EULAR) response was achieved by 46.1% of patients, good EULAR response by 35.98% and remission (Disease Activity Score-28 Joints-C-reactive protein [DAS28-CRP]<2.6) by 32.47%. A gradual increase in efficacy was observed between months 2 and 6. No difference was evident in the rates of response whether patients were on MTX- or leflunomide monotherapy or on combination of MTX with nbDMARDs. Furthermore, no difference in efficacy was observed depending on the use of

glucocorticoids or on the MTX dose in those receiving MTX. Finally no safety variations were evident whether golimumab was administered along with MTX or leflunomide (18).

Ankylosing spondylitis

GO-RAISE was a randomised double-blind placebo-controlled clinical trial during which patients with active AS classified according to the 1984 New York criteria (19) were randomly assigned to receive golimumab 50 mg/4 weeks, golimumab 100 mg/4 weeks or placebo. Significantly more patients in the golimumab 50 mg or 100 mg groups achieved a 20% improvement according to the Assessment of SpondyloArthritis international Society (ASAS) criteria at 14 weeks (primary endpoint), as well as at 24 weeks than patients on placebo. Moreover, both golimumab groups achieved significantly more often an ASAS 40, ASAS 5/6 response and ASAS partial remission both at week 14 and week 24 in comparison to the placebo group (20). After week 24, patients in the placebo group could switch to golimumab in a long-term extension of the trial, which remained blinded as regards the golimumab dosage (50 mg or 100 mg) till week 104 and went on open-label up to 5 years overall. Out of the 355 initially treated patients 254 (71.5%) remained on the drug until week 252 and 101 withdrew (of whom 33 due to adverse events and 35 due to loss of efficacy). As shown in Figure 1D, golimumab retained its effectiveness in a significant proportion of patients who received the drug continuously for 5 years (21-22).

As regards imaging, at week 14 both golimumab doses produced a statistically greater suppression of inflammation on spinal magnetic resonance imaging (MRI) compared to placebo, while the effectiveness of the drug was maintained on repeat imaging at week 104 (23). However, in terms of structural/bone damage, the continuous treatment with either dose of golimumab (50 mg or 100 mg) for 3.5–4 years could not halt radiographic progression as expressed with the modified Stoke AS spinal score (mSASSS) (24). This is in line with the experience gained with the older TNF-α inhibitors (25-27), although recent data imply that long-term -beyond 4 years- inhibition of TNF-α with infliximab in AS patients might be associated with an ultimate decline in the rate of radiographic progression (28). Certainly, this remains to be confirmed through the long-term follow-up of larger groups of AS patients treated with other TNF-α blockers as well, golimumab included.

Concerning the rest of the spondyloarthritis manifestations (inflammatory bowel disease, acute anterior uveitis) some new data has been published regarding golimumab. Firstly, based on the results of randomised double-blind placebo-controlled phase 2 and 3 clinical trials, golimumab has been shown to be effective for the induction and maintenance of remission in patients with ulcerative colitis despite conventional therapy (29-30). Furthermore, in 2013 both the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) approved the use of golimumab (although at a different dosage than the rheumatologic indications) for patients with moderately to severely active ulcerative colitis who have shown inadequate response or intolerance to conventional treatments (2).

On the other hand, acute anterior uveitis is one of the most frequent extra-skeletal manifestations of spondyloarthritis with a prevalence in AS as high as 33% (31). Therapeutically, TNF-α blockers have been successfully employed after failure of topical ophthalmological treatments. However, although the effectiveness regarding the axial skeletal manifestations of AS is comparable among the three older TNF-α inhibitors, it appears that monoclonal anti-TNF-α antibodies (infliximab, adalimumab) are more efficacious compared to the soluble receptor construct (etanercept) in preventing relapses of acute anterior uveitis (32-33). While experience with golimumab in the treatment of spondyloarthritis-associated uveitis is still limited, there have been case reports and retrospective studies describing successful use of golimumab in patients with uveitis that had been resistant to other TNF-α blockers (34-36).

Psoriatic arthritis

Golimumab has been tested in patients with active PsA despite the use of nb-DMARDs or NSAIDs in the context of a randomised double-blind placebo-controlled clinical trial, GO-REVEAL. In this study, patients were randomly assigned to receive golimumab 50 mg/4 weeks, golimumab 100 mg/4 weeks or placebo. At 14 weeks, 51% of patients on golimumab 50 mg and 45% of those on golimumab 100 mg achieved an ACR 20 response (primary endpoint), compared to 9% of patients in the placebo group ($p<0.001$ for both comparisons). Similar differences were observed for ACR 50 and ACR 70 response as well, while the benefit produced by golimumab was still evident at week 24. Moreover, the patients in the golimumab groups did better in terms of enthesitis, the extent and severity of skin involvement and nail disease (37-38). After week 24, patients on placebo could switch to golimumab in an extension of the trial which remained blinded as regards the golimumab dosage (50 mg or 100 mg) until week 52 and went on open-label up to a total of 5 years.

Of the 405 initially randomised patients, 335 continued until week 104 and 279 (68.9%) up to week 252. The drug was discontinued due to adverse events by 12% of patients. As shown in Figure 1E, golimumab produced a sustained benefit in patients who remained on treatment, which included both the joints and the skin throughout the 5-year interval. Furthermore, during the initial 104 weeks the radiographic progression was slower in patients receiving golimumab, particularly in combination with MTX. However, the clinical benefit was comparable either with or without MTX (39-41).

Summarising the long-term results of the GO-FORWARD, GO-RAISE and GO-REVEAL studies from the perspective of patient-reported outcomes, it appears that the management of all three diseases with golimumab continuously for 5 years produced a sustained improvement in function, maintenance of working capability in over 95% of patients and further restoration of the ability to work in a significant proportion of those who had previously lost

it, while, at the same time, there was a decline in the use of healthcare services (42).

Table I. Summary of the incidence of adverse events (AE) during the double-blind phase of the initial randomised clinical trials of golimumab, as well the open-label GO-MORE study. Data are for week 24 of every study and for patients who had received golimumab 50 mg monthly or placebo.

Trial	Golimumab 50 mg		Placebo	
	All AE	Serious AE	All AE	Serious AE
GO-BEFORE	81.6	6.3	72.5	6.9
GO-FORWARD	41	4.2	66.4	3.7
GO-AFTER	66	7	72	10
GO-RAISE	84.8	3.6	76.6	6.5
GO-REVEAL	68	2	59	6
GO-MORE	56	5.7	-	-

Values are %.

Long-term safety

In general, the adverse event profile of golimumab is similar to that of the rest of the TNF-α inhibitors. During the double-blind phase of the placebo-controlled clinical trials, the incidence of adverse events in the groups that received 50 mg golimumab ranged between 41% and 85% and the serious adverse events at 2-7% (Table I). The most common adverse events were infections, mainly upper respiratory tract infections, the vast majority of which were assessed as non-serious. Injection site reactions were reported by less than 5-6% of patients on golimumab 50 mg, rarely were serious and never led to drug discontinuation (4, 6, 7, 20, 37). Later, during the extensions of the trials for up to 5 years of exposure to golimumab, as well as through the large GO-MORE study no new safety signal emerged. Particularly the rates of serious infections (per 100 patient-years, 95% confidence interval [CI]) during the first 2 years for patients on golimumab 50 mg were: GO-BEFORE 4.28 (2.45–6.95), GO-FORWARD 2.24 (0.9–4.62), GO-AFTER 5.79 (3.24–9.95), GO-RAISE 0.93 (0.19–2.72), GO-REVEAL 0.84 (0.17–2.45) (8-9, 13-14, 16-17, 21-22, 39, 41). Of note, among the above-mentioned infections 15 cases of tuberculosis are included, despite that all patients had been screened for tuberculosis and in case of latent infection were treated appropriately.

The rates of anti-golimumab antibodies up to 5 years of follow-up was 7.7–9.7% in the RA trials (9, 14, 17) and 6% in the GO-REVEAL (41). Data for GO-RAISE are available only for 24 weeks (20), when 4.1% of patients were tested positive to anti-golimumab antibodies. In a meta-analysis on the rates of anti-anti-TNF-α antibodies across all indications, which included 2 golimumab trials, the rate of anti-golimumab antibodies was estimated to 4%. Contrary to infliximab and adalimumab, the presence of anti-drug antibodies did not appear to affect clinical effectiveness, although this may be due to the small amount of available data for golimumab (43). On the other hand, in a small series of patients with RA who were treated with golimumab a borderline significant correlation between the drug levels and the observed clinical effectiveness was noted. In this same group of patients, anti-golimumab antibodies were detected in 3 out of 38 patients who did not respond clinically and in whom the drug levels were also low or undetectable (44).

Comparison to other biologics

Up to now, direct comparisons between golimumab and other biologic agents within the frame of a clinical trial have not been performed in any of the rheumatologic indications. However, golimumab has been included in the most recent systematic reviews, meta-analyses and indirect comparisons as regards the efficacy and safety of biologic agents in patients with RA, AS and PsA. Several meta-analyses have been published concerning the efficacy and safety of biologic drugs in patients with RA who have failed nbDMARDs and/or TNF-α blockers (45-52). In general, these meta-analyses point out certain variations across the different biologic agents as regards one or more of the diverse endpoints that the comparisons had focused on. Indeed, in patients with RA who had failed MTX, Schmitz *et al*. found that golimumab was no different than infliximab or adalimumab in producing ACR 20 and ACR 50 response after 6 months, although it was less efficacious than etanercept regarding ACR 20 response and certolizumab pegol as regards ACR 20 and ACR 50 responses (48). However, Kristensen *et al*. in a meta-analysis of 5 studies in RA patients with previous failure to MTX, found that golimumab 50 mg had the highest benefit-to-risk ratio with a proportion of 235 benefited patients against 1 who discontinues due to adverse events, while the respective proportions for certolizumab pegol, abatacept and tocilizumab were 13:1, 12:1 and 11:1 (51). Furthermore, concerning RA patients who had failed to a previous TNF-α blocker, Schoels *et al*. concluded that patients on golimumab were significantly less likely to achieve an ACR 20 response (but not ACR 50 or ACR 70) at 6 months compared to rituximab, abatacept or tocilizumab, but were also less likely to experience adverse events (46). From the patients' perspective, three meta-analyses and indirect comparisons focused on the improvement of the HAQ score conferred by different biologics. In all three of them, golimumab turned out to be at least as effective as other biologics in improving HAQ in patients with RA whether they had never received or had failed to MTX/DMARDs (45, 48, 52).

Regarding safety, a meta-analysis showed that golimumab was not associated with an increased risk of discontinuation due to adverse events as compared to placebo, while the rest of the monoclonal anti-TNF-α antibodies had an increased risk and etanercept a reduced risk (always with relation to the respective placebo treatments) (47). Finally, among RA patients who are benefited by the US public healthcare system (Medicare) and had been

prescribed biological treatment during the previous years, it appears that the risk for hospitalisation due to infection (taking abatacept as a reference) was greater with infliximab, etanercept or rituximab, but not with golimumab, adalimumab, certolizumab pegol or tocilizumab (53).

In AS a recent meta-analysis and indirect comparison of all TNF-α inhibitors, except certolizumab pegol, could not demonstrate significant differences among the various drugs at the approved dosages as regards efficacy (ASAS 20) at 3 months (54).

Concerning PsA, a meta-analysis and indirect comparison of all TNF-α blockers (except certolizumab pegol), which used infliximab as a reference, showed that golimumab and adalimumab were not significantly different than infliximab in all endpoints examined (ACR 20/50/70, Psoriatic Arthritis Response Criteria [PsARC] at 3 or 6 months), while etanercept was less effective than infliximab in ACR 70 response at week 24. With relation to the skin, infliximab was better than golimumab and adalimumab in terms of Psoriasis Area and Severity Index (PASI) 50% response at month 3, but no more so as regards PASI 50 or 75 at month 6. On the contrary, etanercept was less efficacious in achieving PASI 50 and 75 responses at 6 months compared to infliximab. The incidence of the most common adverse events was also similar across all biological agents examined, although etanercept was associated significantly more often with injection site reactions compared to adalimumab and golimumab (55). However, another meta-analysis and indirect comparison of the same TNF-α blockers could not show significant differences regarding efficacy in PsA (56).

An issue of controversy has been the potential association between TNF-α blockade and malignancy. Five meta-analyses have been published to date which address the risk of malignant disease in general or of specific types of cancer with the use of TNF-α blockers, including golimumab: three in RA patients (57-59), one in PsA (60) and one across all indications (61). None of those studies has demonstrated a significantly increased risk for neoplasia, whereas none of the agents reviewed seems to be associated with a different risk of cancer compared to the others. As data on cancer incidence with ongoing exposure to TNF-α blockers are continuously caught in plenty of national registries, it is expected that in the future safer conclusions will be reached regarding all biologics as a group, as well as each one in particular. Finally, a measure of the efficacy-to-safety balance of a therapeutic agent is the proportion of patients remaining on treatment over time. Although details on exposure to biological agents are systematically collected in registries, data about golimumab have been reported only from the Swedish registry. In this report, golimumab survival over 24 months was 56% for biologic-naïve RA patients, 52% for RA patients who had been previously exposed to 1 or 2 other biologic agents and 32% for those who had a previous experience of 3 or more biologics. The respective rates for AS were 65%, 57% and 40% and for PsA 56%, 51% and 53%. In RA and AS, survival was higher, when golimumab had been prescribed as the first biologic and lowest when prescribed as the third one and beyond, although this trend reached significance only in the RA group which, besides, was the most populous one (62).

Conclusion

Being the newest fully human monoclonal antibody against TNF-α and after more than 4 years since it was first made available in Europe and the US for the treatment of RA, AS and PsA, golimumab comes of age. The long-term extensions of the initial randomised clinical trials, the open-label trial of golimumab in thousands of RA patients in settings close to the everyday clinical practice, the first data from registries, the ongoing scientific research and the first systematic reviews of the literature that include golimumab enrich our knowledge about the drug. Indeed, it appears that golimumab possesses the properties of a monoclonal TNF-α-blocking antibody, both as regards its efficacy, as well as its adverse event profile. The relatively limited and often conflicting differences that emerge in the indirect comparisons with the other biologics, considering also the variations in the methodologies employed, do not allow to safely conclude whether one or another TNF-α blocker is better than the others. Therefore, the choice of a biologic drug should be individualised, taking into account the patient profile, but also the patient preferences. From this perspective, the subcutaneous once monthly self-administration perhaps represents an advantage to patients who tend to prefer therapies that cause least disturbance of their everyday routine and carry a safety profile that is sufficiently known (63).

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