EFFICACY AND SAFETY OF GOLIMUMAB AS ADD-ON THERAPY TO DISEASE-MODIFYING ANTIRHEUMATIC DRUGS IN RHEUMATOID ARTHRITIS: RESULTS OF THE GO-MORE STUDY IN ROMANIA

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Abstract

Objectives. GO-MORE was an open-label, multinational, prospective observational study in patients with active rheumatoid arthritis (RA) in typical clinical practice settings in 40 countries. The trial involved patients with active rheumatoid arthritis despite treatment with disease modifying antirheumatic drugs (DMARDs) and naïve to biological agents. Considering the different countries demographic or disease characteristics, we analysed the efficacy and safety data of the Romanian subpopulation in this paper.

Method. The patients received subcutaneous GOL 50 mg once a month for a period of 6 months. The primary endpoint was the percentage of patients with a good and moderate EULAR DAS28-ESR response after 6 months of treatment.

Results. A total of 51 patients with active RA with an average disease duration of 3.53 years and an average DAS28 of 6.15 at baseline were included. All patients were taking DMARDs (66% patients were taking methotrexate (MTX) and 23.5% leflunomide (LEF) in monotherapy; the others were taking other background therapies or combinations of them). All these 51 patients received GOL 50 mg once a month. After 6 months 78.4% of patients showed a good or moderate EULAR response, most of them (68.6%) after the first administration; 27.5% showed low DAS28-ESR and 7.8% were in remission. GOL was well tolerated and the safety profile was consistent with the findings of previous studies. The number of serious side effects (12%) or which lead to discontinuation of therapy (8%) was generally low.

Conclusions. The addition of subcutaneous GOL 50 mg once a month to different DMARDs in patients with active RA yielded a moderate or good EULAR DAS28-ESR response after 6 months in a proportion of 78.4% of patients in Romania. The response was observed after the first administration of GOL. The safety profile is consistent with other clinical trials with antiTNFi in RA with no new safety signals detected.

Keywords: DMARDs (biologic), methotrexate, rheumatoid arthritis

INTRODUCTION

Over the last years the objectives of treatment in RA have changed and became more ambitious. The primary target is to reach and maintain clinical remission or at least low disease activity and to prevent the progression of structural damage and disability (1-3). The necessary steps for reaching the target are very well established. Treatment begins
with disease modifying antirheumatic drugs (DMARDs), most commonly with MTX. Patients with inadequate response to DMARDs in an appropriate dose can be considered for treatment with biological therapy (1-3). Most pivotal clinical trials with anti-TNF therapy were carried out in combination with MTX in patients inadequately responding to MTX (4-6). The experience of using combination with other DMARDs is limited. Since in clinical practice a percentage of patients do not receive MTX as DMARD, or receive it at doses different from those prescribed in clinical trials, it is important to obtain information on the efficacy of anti-TNF-alpha drugs in patient populations more similar to those treated in clinical practice, and to evaluate the patients using efficacy measures more consistent with those employed in routine practice.

Golimumab (GOL) is an anti-TNF monoclonal antibody that has shown clinical efficacy in a broad range of clinical trials in RA, being administered in patients naïve to MTX (GO-BEFORE), after MTX failure (GO-FORWARD) or anti-TNF-alpha experienced (GO-AFTER) (7-9) and inhibits joint lesion progression as assessed by conventional radiology (10).

GO-MORE was an open-label, multinational, prospective study in patients with active RA in typical clinical practice settings. In part 1, patients received as add-on to DMARDs monthly 50-mg subcutaneous golimumab for 6 months. The percentage of patients with good/moderate European League Against Rheumatism (EULAR) 28-joint disease activity score (DAS28)-erythrocyte sedimentation rate (ESR) response was compared in patient subgroups with various concurrent or previous DMARD treatments. In part 2, patients with EULAR responses but not remission were randomly assigned to receive IV+SC or subcutaneous GOL to month 12; DAS28-ESR remission was measured.

GO-MORE trial comprised 3280 patients with active RA from 40 countries and from various geographical areas covering all continents. Some demographic or disease characteristics at baseline, different from one center to another, respectively from one continent to another, could provide interesting data about territorial differences. The aim of this paper is to describe the efficacy and safety of subcutaneous GOL in the Romanian subgroup of patients in the first part of the GO-MORE trial.

**PATIENTS AND METHOD**

Part one of the GO-MORE trial was an open, multicentre, international prospective trial (protocol P06129; NCT00975130) for evaluation of efficacy and safety of GOL subcutaneous once a month in patients with active RA despite treatment with DMARDs and naïve to biological agents (11). The study was approved by the Ethics Committees of participating hospitals and was carried out following the Good Clinical Practice guidelines and the Declaration of Helsinki (11). The enrolment was performed within October 2009 – July 2011 and included patients aged 18 years or older with RA (according to the revised criteria of the American College of Rheumatology 1987), naïve to biologic therapy and with active disease (DAS28-ESR score ≤ 3.2) despite treatment with at least one of the following DMARDs: MTX, sulphasalasine (SSZ), hydroxychloroquine (HQ), leflunomide (LEF), gold salts, azathioprine (AZA) or cyclosporine (CyA), in monotherapy as well in combination. The DMARDs doses had to be stable at least 1 month before entering in the trial and maintained stable for entire follow-up period. During the study the use of corticosteroids was possible but not mandatory maintaining a stable dose. The patients were biologically naïve and the evaluation of tuberculosis risk as well as the chemoprophylaxis was performed according to local recommendations. Patients with active tuberculosis, untreated latent tuberculosis, moderate to severe heart failure (class III or IV),lymphoproliferative disease or visceral neoplasm over the last 5 years or any other contraindication to anti-TNF-alpha treatment were excluded (11).

In part 1 of GO-MORE enrolled, eligible patients received subcutaneous GOL 50 mg on the same day every month for 6 months, being evaluated 5 times (screening, baseline, beginning of 2nd month, respectively 4th month and at the end of 6th month) in the followed-up period. The DMARDs and corticosteroids doses remained stable throughout the study. The evaluation was made before the administration of the next GOL dose and at the end of month 6. The second part of the study was not carried out in Romania.

The primary efficacy endpoint was the percentage of patients with a good or moderate EULAR DAS28-ESR response after 6 months of treatment (defined as an improvement in DAS28-ESR score of ≥ 1.2 versus the baseline score, or from 0.6 to 1.2 in those with a baseline score of ≥ 5.1). Secondary var-
iables included the percentage of patients with low disease activity (DAS28-ESR and DAS28-CRP score ≤ 3.2), the percentage achieving clinical disease remission (DAS28-ESR and DAS28-CRP score <2.6), and clinical efficacy according to the Simplified Disease Activity Index (SDAI – Low disease activity: SDAI ≤11; remission: SDAI ≤ 3.3). Achievement of minimal or no functional impairment (HAQ-DI score ≤ 0.5 [Health Assessment Questionnaire Disability Index]) was also assessed. The evaluation of safety was made by reporting all adverse reactions.

RESULTS

Demographic data

The Romanian study population consisted of 51 patients: 48 women (94.1%) and 3 men (5.9%). The average age was 57 years old (24-78 years old). The average disease duration was 3.53 years, with 31% of patients having a recent disease (< 2 years) and 21% having disease over 10 years (range 0.08 to 30 years).

The mean baseline disease activity was 6.15 and 5.41 as measured by DAS28-ESR, and DAS28-CRP, respectively. Out of 51 patients, 44 (86.27%) had high disease activity at baseline and only 7 had moderate activity. The patients also had an average pain score at onset of treatment of 71.84 (on a scale from 0-100 mm) and a high fatigue index. Other activity parameters are presented in table 1 compared to the baseline results of the overall population of GO-MORE (3280 patients).

As prior treatment to GOL, 34 patients (66%) were receiving MTX as monotherapy in almost 50% of patients and combined with other drugs for the rest (Table 2). Most of the patients were receiving high doses of MTX (15 mg/week). 12 patients (23.5%) were receiving LEF and 6% other DMARDs. Corticosteroids treatment was used in 37.3% of patients. Over 70% had experienced failure with more than one DMARD (Table 2).

TABLE 2

| Patient characteristics: part 1 | Romania (N=51) | Total (N=3280) |
|--------------------------------|----------------|----------------|
| Treatment history |                |                |
| Concomitant methotrexate (MTX) dose | n=51 | n=3,280 |
| Any dose, n (%) | 34(66.7) | 2,663 (81.2) |
| Low (<10 mg/week), n (%) | 2 (3.9) | 142 (4.3) |
| Medium (>=10 and <15 mg/week), n (%) | 6 (11.8) | 526 (16.0) |
| High (>=15 mg/week), n (%) | 26 (51.0) | 1,995 (60.8) |
| Concomitant corticosteroid use | n=51 | n=3,280 |
| Received corticosteroids, n (%) | 19 (37.3) | 2,078 (63.4) |
| DMARD monotherapy or combination | N=51 | n=3,270 |
| MTX only, n (%) | 16 (31.4) | 1,681 (51.4) |
| MTX + HQ, n (%) | 4 (7.8) | 433 (13.2) |
| MTX + LEF, n (%) | 6 (11.8) | 216 (6.6) |
| MTX + SSZ, n (%) | 3 (5.9) | 150 (4.6) |
| MTX + HQ + SSZ, n (%) | 4 (7.8) | 106 (3.2) |
| LEF only, n (%) | 12 (23.5) | 303 (9.3) |
| Other DMARD combinations, *n (%) | 3 (5.9) | 381 (11.7) |
| No of DMARD failed | n=51 | n=3279 |
| 1, n (%) | 14 (27.5) | 1,129 (34.4) |
| 2, n (%) | 18 (35.3) | 1,176 (35.9) |
| >=3, n (%) | 19 (37.3) | 974 (29.7) |

Efficacy results

After 6 months of GOL treatment 78.4% (40/51) of patients achieved good or moderate EULAR DAS28-ESR response. Treatment response was rapid, with 68.6% (35/51) of patients showing EULAR good or moderate response at month 2, after a single dose of GOL (Figure 1).

At month 2, 4 and 6, DAS28-ESR remission were 7.8%, 9.8% and 7.8%, respectively (Figure 2), DAS28-ESR low disease activity were 11.8%, 23.5% and 27.5% respectively (Figure 2), SDAI remission were 2.0%, 2.0% and 7.8% respectively (Figure 3) and SDAI low disease activity were 23.5%, 31.4% and 47.1%, respectively (Figure 3).

The subgroups efficacy analysis depending on the presence or absence of corticosteroids therapy or MTX, the number of previously failed DMARDs, the type of DMARDs or MTX only compared to MTX-combination with other DMARDs did not identify statistically significant differences between subgroups. Still there was a tendency towards better
response in patients who had MTX compared to other DMARD and especially in those who had high doses of MTX. The response was better in patients with MTX only versus MTX-combination, but the difference was not statistically significant. Also, patients not receiving corticosteroids had a numerically higher in terms of DAS28-ESR EULAR response rate compared to those who received corticosteroids, but the difference was not statistically significant. (Figure 4). There were no differences in response between the patients who had failed one or more DMARDs.

HAQ-DI improved after 6 months of GOL treatment with minimal or no functional impairment achieved in 31.3% of patients.

**FIGURE 1.** Percentage of patients achieving EULAR good or moderate response. The evaluations were made at the start of the second month of therapy (after a single dose of golimumab), at the start of the fourth month (after 3 doses), and at the end of the sixth month (after 6 doses; primary endpoint).

**FIGURE 2.** Percentage of patients with DAS28-ESR remission and with DAS28-ESR low disease activity

**FIGURE 3.** Percentage of patients with SDAI remission and with SDAI low disease activity
Tolerability and safety

GOL was well tolerated. The safety profile was consistent with the data from prior studies of GOL. At least one adverse event was documented in 21 patients (40%) half of them (21%) were considered to be study drug related. The most common adverse event system organ class was infections (17%). Serious treatment emergent adverse events occurred in 6 (11.5%) of patients and in 4 patients (7.6%) the medication had to be discontinued because of adverse reactions. No deaths and no injection site reactions were reported (Table 3) and < 10% of patients showed clinically significant abnormal laboratory values. The later were not severe and did not necessitate discontinuation of study medication.

DISCUSSIONS

The analysis of the patients recruited in Romania in the GO-MORE study showed that treatment with subcutaneous GOL 50 mg monthly for 6 months resulted in a good or moderate EULAR DAS28-ESR response in 78.7% of patients. This number is comparable with 82.1% achieved in the overall GO-MORE population (3,280 patients) (11). The response manifested early (after the first dose of GOL) with 68.6% of patients achieving good or moderate EULAR response at the beginning of month 2 in the Romanian subpopulation compared to 64.3% in the global study population. Some numerical differences between the Romanian subpopulation and the global study population were seen for disease activity evaluated by DAS28-ESR after 6 month, where the percentage of patients in Romania achieving low disease activity (DAS28-ESR score ≤3.2) and remission (DAS28-ESR score <2.6) were 27.5% and 7.8% respectively versus 37.4% and 23.9% respectively (11). Similar results highlight the SDAI evolution. The percentages of patients in Romania achieving SDAI-low disease activity and SDAI-remission were 47.1% and 7.8% versus 48.3% and 14.2%, respectively.
GO-MORE was a multinational study with patients recruited from different geographical areas with different medical practices and different types of patients (11,12). The Romanian patients had higher baseline disease activity and shorter disease duration compared to those of the global population (Table 1). The overall study showed that patients having high disease activity at baseline were less likely to achieve remission than patients having moderate disease activity at baseline, while the duration of disease does not seem to influence significantly the percentage of remission in this trial (Figure 5) (12). Further explanations of the differences in response between the Romanian subpopulation and the overall population may relate to access to biological therapy and differences in the prescription of synthetic DMARDs. In our subgroup, 66.7% of patients were receiving MTX in monotherapy versus 81% in the global one and 33.3% in combination with other DMARDs versus 27% in the global one (LEF in monotherapy: 23.5% versus 9.3% or steroids 37.3% versus 63.4%). Over 70% had experienced failure with more than one DMARD.

As additional findings, there was a tendency to better respond in patients who had MTX compared to LEF (31.5% vs 23%) and especially in those who had high doses of MTX.

GOL was well tolerated in this study. The adverse events occurred in 40% of patients but only half of them were considered to be study drug related, only few were serious and very few determined discontinuation of medication.

The main limitation of our study is its sample size (51 efficacy evaluable patients).

In conclusion, the results of GO-MORE study in Romania show that GOL is effective in combination with different DMARDs in patients with RA presenting failure of one or more DMARDs but naïve to biologics, exhibiting a good or moderate EULAR DAS28-ESR response in a majority of patients (78.4%). The onset of action was rapid, with good tolerability, and a safety profile consistent with that described for GOL in other clinical trials and in the Summary of Product Characteristics.

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REFERENCES
1. Smolen J.S., Landewe R., Breedveld F.C., Buch M., Burmester G., Dougados M., Emery P. EULAR
2. recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: update. Ann Rheum Dis 2013; 0:1-18
3. Smolen J.S., Landewé R., Breedveld F.C., Dougados M., Emery P., Gaujoux-Viala C., et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010; 69:964-75
4. Smolen J.S., Aletaha D., Bijlsma J.W., Breedveld F.C., Boumpas D., Burmester G., et al. T2T Expert Committee. Treating rheumatoid arthritis to target: Recommendations of an international task force. Ann Rheum Dis 2010; 69(4):631-637
5. Klareskog L., van der Heijde D., de Jager J.P., Gough A., et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet, Vol. 28, 2004; 363(9410):675-81
6. Maini R.N., Breedveld F.C., Kalden J.R., Smolen J.S., et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41(9):1552-63
7. Breedveld F.C., Weisman M.H., Kavanaugh A.F., Cohen S.B., et al. 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 methotrexate treatment. Arthritis Rheum 2006; 54(1):26-37
8. Emery P., Fleischmann R.M., Moreland L.W., Hsia E.C., Strusberg I., Durez P., et al. Golimumab, a human antitumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naïve patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009; 60(8):2272-2283
9. Keystone E.C., Genovese M.C., Klareskog L., Hsia E.C., Hall S.T., Miranda P.C., et al. Golimumab, a human antibody to tumour necrosis factor alpha given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009; 68(6):789-796
10. Smolen J.S., Kay J., Doyle M.K., Landewe R., Matteson E.L., Wollenhaupt J., et al. GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009; 374(9685):210-221
11. Emery P., Fleischmann R., van der Heijde D., Keystone E.C., Genovese M.C., Conaghan P.G., et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. Arthritis Rheum 2012; 63:1200-10. Erratum in: Arthritis Rheum 2012; 64:1045
12. Combe B., Dasgupta B., Louw I., Pal S., et al. on Behalf of the GO-MORE Investigators – Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study. Ann Rheum Dis 2014; 73:1477-1486
13. Durez P., Pavelka K., Lazaro M., et al. Remission rates during golimumab treatment for rheumatoid arthritis are associated with differences in baseline disease states across geographic regions in the GO-MORE study. Ann Rheum Dis 2013; 72 Suppl 3:872