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

Simona Rednic[1], Magda Parvu[2], Catalin Codreanu[3], Ioan Ancuta[4], Maria Suta[5], Anca Rosu[6], Rodica Chireac[7], Lorena Petcu[8], Ruxandra Ionescu[9]

[1]Rheumatology Department, Emergency County Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca
[2]Rheumatology Department, Colentina Clinical Hospital, Bucharest
[3]Dr. Ion Stoia Center for Rheumatic Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest
[4]Internal Medicine and Rheumatology Department, Dr. Cantacuzino Clinical Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest
[5]3rd Clinical Department, Faculty of Medicine, Ovidius University, Constanta
[6]Rheumatology and Internal Medicine Department, University of Medicine and Pharmacy, Craiova
[7]Clinical Rehabilitation Hospital, Gr. T. Popa University of Medicine and Pharmacy, Iasi
[8]Merck Sharpe & Dohme Romania, Bucharest, Romania
[9]Rheumatology and Internal Medicine Department, Sf. Maria Clinical Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest

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 month 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

Correspondence address:
Lorena Petcu, Merck Sharpe & Dohme Romania, Bucharest, Romania
E-mail: lorena.petcu@merck.com

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 3.2) despite treatment with at least one of the following DMARDs: MTX, sulfasalasine (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).

TABLE 1

Demographic characteristics	**Romania (N = 51)**	**Total (3,280)**
Gender Women Men	 48 (94.1%) 3 (5.9%)	 2,716 (82.8%) 564 (17.2%)
Age (years)	57 (24-78)	53 (18-88)
Race Caucasian	 51 (100%)	 2,283 (69.6%)
IMC (kg/m^2) median (min-max)	 27.02 (18.5-42.4)	 26.2 (14.0-54.5)
Disease characteristics		
Disease duration, years Median (min, max)	3.53 (0.08, 30.90)	4.9 (0.01, 56.6)
TJC28, mean (SD)	13.9 (5.68)	13.0 (6.81)
SJC28, mean (SD)	8.3 (3.92)	9.6 (5.56)
DAS28-ESR	6.15 (0.783)	5.97 (1.095)
DAS28-CRP	5.41 (0.740)	5.41 (0.998)
CRP (mg/l)	10.57 (15.284)	14.48 (20.376)
ESR (mm/h)	37.1 (22.23)	34.9 (24.64)
Patient assessment of Pain (0-100 mm)	71.84 (26-100)	
Fatigue (1-4)	3.04 (2-4)	
HAQ-DI, mean (SD)	1.45 (0.67)	1.44 (0.67)

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 l, 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).*

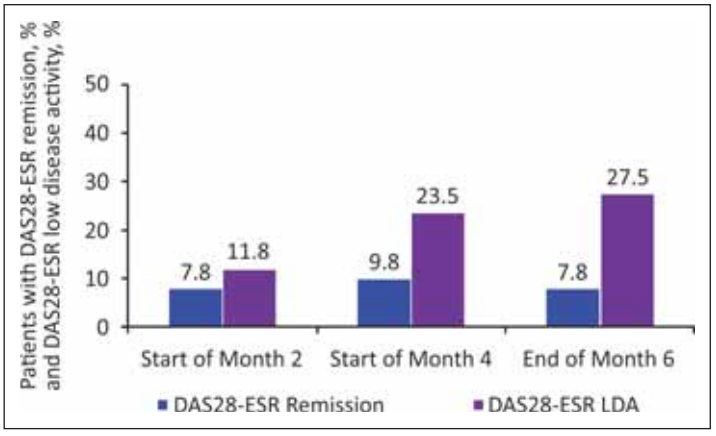

FIGURE 2. *Percentage of patients with DAS28-ESR remission and with DAS28-ESR low disease activity*

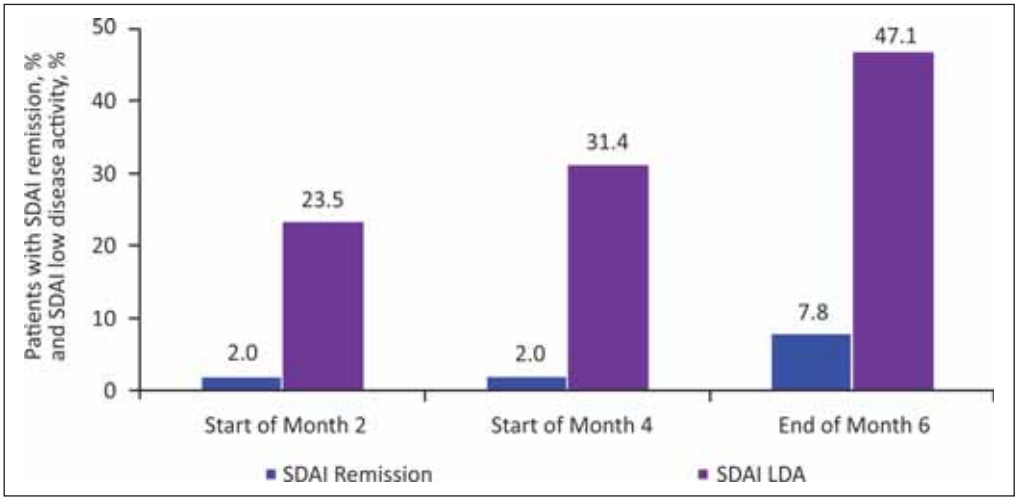

FIGURE 3. *Percentage of patients with SDAI remission and with SDAI low disease activity*

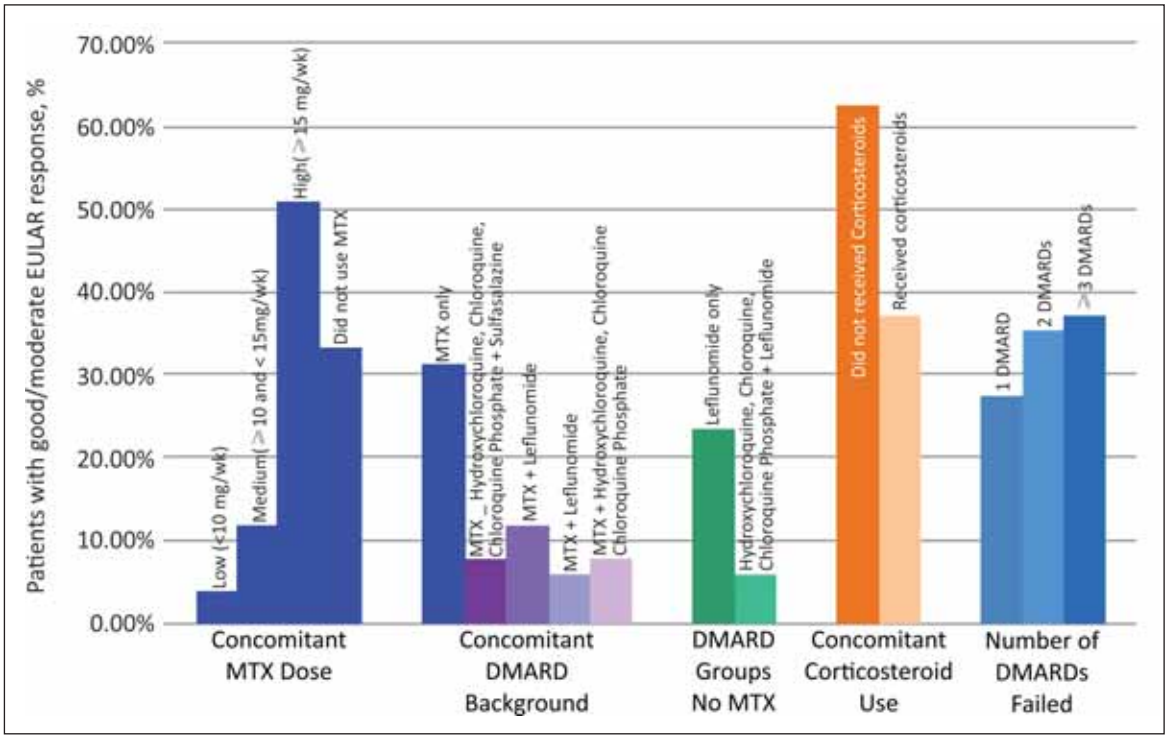

FIGURE 4. *The percentage of patients with good or moderate DAS28-ESR EULAR response at end of month 6 by different concomitant MTX doses, by different concomitant DMARDs, by the concomitant corticosteroid (CS) use and by the number of previously failed DMARDs*

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.

TABLE 3

Subjects with treatment emergent adverse effects (TEAE)	Number of subjects (%)
One or more TEAE	21 (40.38%)
TEAE possibly or probably related to study medication	11 (21.15%)
Serious TEAE	6 (11.54%)
TEAE leading to early withdrawal	4 (7.69%)
Deaths	0
Injection site reactions	0
Clinically significant abnormal lab values	5 (9.62%)

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.

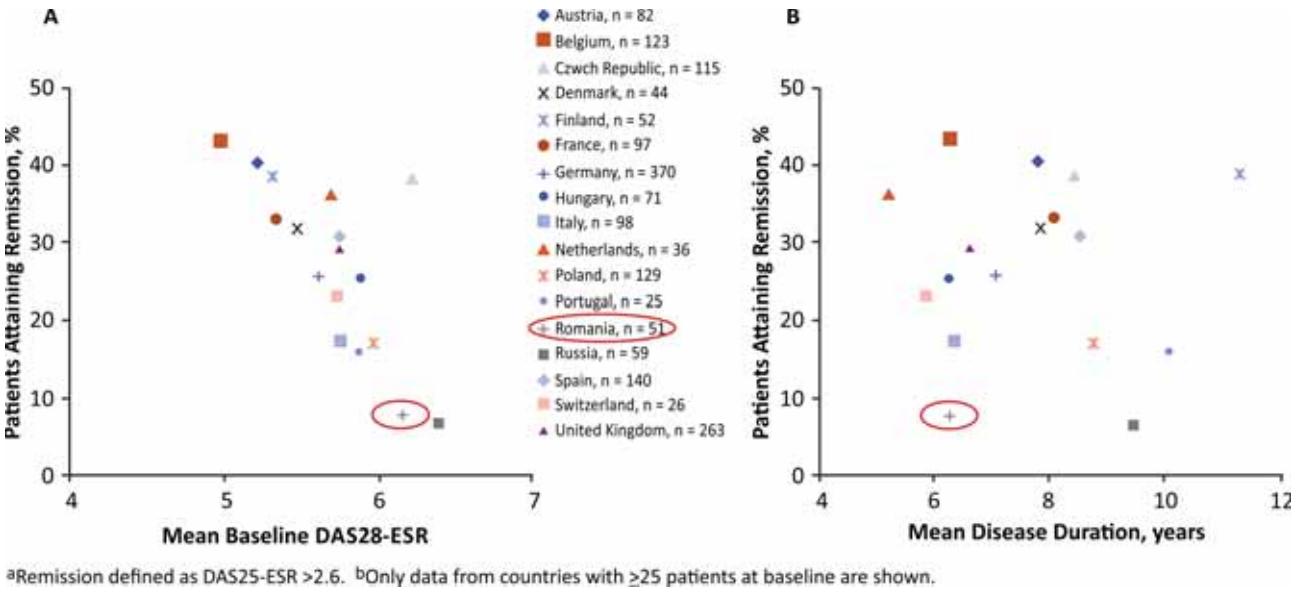

FIGURE 5. *Relationships between baseline disease activity, disease duration, and remission after 6 months add-on GLM in European countries*

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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