What could we learn from the sub-analysis of a single nation cohort in a worldwide study? Lessons from the results observed in the Italian cohort of the GO-MORE trial

R. Giacomelli[1], P. Ruscitti[1], S. Bombardieri[2], G. Cuomo[3], S. De Vita[4], M. Galeazzi[5], M. Mecchia[6], on behalf of the Italian GO-MORE Investigators

[1]Rheumatology Unit, Department of Biotechnological and Applied Clinical Science, School of Medicine, University of L'Aquila, Italy; [2]Rheumatology Unit, University of Pisa, Italy; [3]Rheumatology Unit, Second University of Naples, Italy; [4]Rheumatology Clinic, Department of Medical and Biological Sciences, University Hospital "Santa Maria della Misericordia", Udine, Italy; [5]Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, University of Siena, Italy; [6]MSD Italy, Rome, Italy.

Abstract

Objective

GO-MORE Trial investigated the use of Golimumab (GLM) in 3280 rheumatoid arthritis (RA) patients worldwide. At present, the burden of arthritis is greater in poorer countries than in developed countries due to socioeconomic disparities, thus suggesting the usefulness of subgroup investigations.

We aimed to evaluate GLM as add-on therapy for RA patients in the Italian cohort of GO-MORE trial and compared the clinical characteristics between Italian patients and the enrolled patients worldwide.

Methods

Ninety-eight Italian patients with active RA, fulfilling the 1987 ACR criteria were enrolled. Statistical analyses were performed to assess: i. the differences in baseline characteristics; ii. the efficacy after 6 months; between Italian and Rest of the World GO-MORE populations.

Results

Compared to the worldwide population, Italian patients showed a lower value of disease activity and a significantly short disease duration. Unlike the worldwide patients, the large majority of Italian patients received biologic therapy after the failure of the first synthetic DMARD and were not treated by high methotrexate dosage. After 6 months of GLM treatment, no differences were observed in the therapeutic response. Italian patients reported a positive autoinjection experience mirroring the worldwide results.

Conclusion

The analysis of the Italian GO-MORE subset confirms that differences among patients may be shown, depending on different approaches in different health systems. GLM in the Italian patients showed a favourable benefit/risk profile and the positive autoinjection experience may help with patient's compliance and survival of the treatment.

Key words

rheumatoid arthritis, biologic products, tumour necrosis factor-alpha, golimumab, clinical trial, subset analyses

Roberto Giacomelli, MD, PhD
Piero Ruscitti, MD
Stefano Bombardieri, MD
Giovanna Cuomo, MD, PhD
Salvatore De Vita, MD
Mauro Galeazzi, MD
Monica Mecchia, MD

Please address correspondence to:
Dr Roberto Giacomelli,
Rheumatology Unit,
Department of Biotechnological and Applied Clinical Sciences,
University of L'Aquila, delta 6 building,
67100 L'Aquila, Italy.
E-mail: roberto.giacomelli@cc.univaq.it

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease affecting about 1% of the general population. In genetically susceptible individuals, specific environmental factors may activate the immune system antibody production, which will contribute to the disease development resulting in chronic joint inflammation and systemic complications, with increased comorbidity. Thus, despite increasing use of early and aggressive treatments, RA is still a chronic disorder with clinically important potential comorbidities (1-4). RA may be classified according either 1987 American College of Rheumatology (ACR criteria) or 2010 ACR/European League against Rheumatism (ACR/EULAR) criteria (1-3) and, although both the criteria are widely used, available literature suggests that the previous criteria may identify a subset of RA patients with a higher aggressive disease (3, 4). At present, clinical remission is the main therapeutic goal, especially in RA of recent onset. However, the low disease activity may be considered as an appropriate goal in patients with longstanding RA, and many clinical trials indicated that these goals may be reached in these patients (4).

Although clinical trials are considered to be the ''gold standard'' to compare one treatment with another or with a placebo, several limitations have been identified in the last years. Clinical trials reports generally ignore individual variations and the potential effect in small homogeneous subsets of patients (5, 6). Another limitation concerns their generalisability. Many variables besides the therapies may affect the outcomes such as patients from different countries, followed by different health systems (5, 6). In fact, the management of RA widely varies across Europe and worldwide, considering different drugs management, including the delay in starting synthetic DMARD (sDMARD) therapies, the use of methotrexate (MTX) and the onset of biologic DMARD (bDMARD) therapies (7, 8). Although the clinical status of RA patients significantly improved in recent years than in previous decades, as published by western European and north American researchers, the burden of arthritis appears greater in poorer countries than in more developed countries (9, 10). Taken together, these findings may alert, not only healthcare professionals and designers of health policy, but also the study designers of multicentre worldwide therapeutic trials, because of disparities among countries, still represent an important challenge for the interpretation of data. Thus, the value of dividing RA into subsets has been recognised as a potential strategy to efficiently implement the knowledge about treatments. On these bases, investigators may carry out subgroup analyses to evaluate if the observed effects may differ across baseline characteristics (11, 12).

In this paper, we report the results observed in the Italian cohort of RA patients, enrolled in the GO-MORE Trial (13), involving 3280 patients worldwide, aimed at investigating the use of Golimumab (GLM), a human anti-tumour necrosis factor (TNF) monoclonal antibody, as add-on therapy for RA. In this Trial, GLM induced a good/moderate EULAR response in the majority of patients and 25% out of the enrolled patients, achieved remission after 6 months of therapy (13). The sub-analysis of the Italian cohort was conducted to evaluate the therapeutic outcome in the Italian patients enrolled in the GO-MORE Trial.

Patients and methods

The GO-MORE study was an open-label, multinational, multicentre, prospective trial (ClinicalTrials.gov identifier: NCT00975130) to assess the efficacy and safety of GLM in active RA patients despite sDMARD treatment (13). The enrolled patients received 50 mg GLM for 6 months. the patients continued current sDMARD regimen. EULAR response was measured after 1 month, at month 3 and at the end of month 6. All patients fulfilled the 1987 ACR criteria for RA. The inclusion criteria included: age ≥18 years; an active disease (disease activity score in 28 joints [DAS28]-erythrocyte sedimentation rate [ESR] ≥3.2); the use of at least one allowable sDMARD (MTX, sulfasalazine, hydroxychloroquine,

chloroquine, chloroquine phosphate, leflunomide, gold salts, azathioprine and cyclosporine) at a stable dose for at least 1 month before the trial entry; and the eligibility for TNF inhibitor use, according to local guidelines and investigators' opinion. Exclusion criteria included: evidence of active tuberculosis or untreated latent tuberculosis; history of moderate to severe heart failure; history of lymphoproliferative disease or malignancy within the past 5 years with the exception of non-melanoma skin cancer treated without recurrence; or any other contraindication for TNF inhibitor use. The study received approval from appropriate Research Ethics Committees and was conducted in accordance with the Declaration of Helsinki and standards of good clinical research practice. Details of patients' inclusion/exclusion criteria and informed consent have been described previously (13).

Italian patients

Out of the total 3280 patients from the efficacy population in part 1 of the GO-MORE study, 98 patients with active RA, despite sDMARD therapy, and naïve for bDMARDs were enrolled, in 32 tertiary level rheumatology units in Italy. In this report, Italian refers to these 98 patients and the Rest of the World refers to the other enrolled patients (3182=3280-98, Global patient population minus Italian patient population).

Clinical outcomes

The primary efficacy outcome was the proportion of patients who achieved a good or moderate EULAR DAS28-ESR response at the end of month 6. The following clinical efficacy variables were measured at baseline and after 1, 3 and 6 months of treatment: ESR, C-reactive protein (CRP) levels, 28 tender joint count (TJC28), 28 swollen joint count (SJC28), DAS28-ESR score, proportion of patients achieving good or moderate EULAR response (DAS28-ESR improvement of >1.2 from any baseline score or an improvement of 0.6–1.2 from a baseline score of ≤5.1), proportion of patients in remission (DAS28-ESR <2.6) and with low disease activity (DAS28-ESR ≤3.2).

Table I. Baseline characteristics of the Italian population and Rest of the World population.

Rest of the World results		Italian results	
Female (%)	82.9%	Female (%)	79.6%
Age (years) (mean ± SD)	52.1 ± 12.8	Age (years) (mean ± SD)	55.5 ± 12.4
TJC28 (mean ± SD)	13.0 ± 6.8	TJC28 (mean ± SD)	11.1 ± 6.4
SJC28 (mean ± SD)	9.7 ± 5.6	SJC28 (mean ± SD)	6.5 ± 4.5
ESR mm/h (mean ± SD)	34.7 ± 24.6	ESR mm/h (mean ± SD)	40.4 ± 24.5
DAS28-ESR (mean ± SD)	5.9 ± 1.0	DAS28-ESR (mean ± SD)	5.7 ± 1.0
DAS28-ESR Moderate disease activity (3.2-5.1)(%)	21.3%	DAS28-ESR Moderate disease activity (3.2-5.1)(%)	22.9%
DAS28-ESR High disease activity (>5.1)(%)	78.7%	DAS28-ESR High disease activity (3.2-5.1)(%)	77.1%
CRP mg/L (mean ± SD)	14.4 ± 20.3	CRP mg/L (mean ± SD)	15.9 ± 22.0
DAS28-CRP (mean ± SD)	5.4 ± 1.0	DAS28-CRP (mean ± SD)	5.1 ± 1.0
HAQ-DI (mean ± SD)	1.4 ± 0.6	HAQ-DI (mean ± SD)	1.3 ± 0.7
Disease duration <2 years, (%)	27.4%	Disease duration <2 years, n (%)	36.7%
Disease duration ≥2 and <5 years, (%)	23.3%	Disease duration ≥2 and <5 years, (%)	26.5%
Disease duration ≥5 and ≤10 year, (%)	21.1%	Disease duration ≥5 and ≤10 year, (%)	12.3%
Disease duration >10 years, (%)	28.2%	Disease duration >10 years, (%)	24.5%
1 previous sDMARD (%)	33.6%	1 previous sDMARD (%)	60.2%
2 previous sDMARDs (%)	36.3%	2 previous sDMARDs (%)	24.5%
2 previous sDMARDs (%)	30.1%	2 previous sDMARDs (%)	15.3%
Any concomitant dose of MTX	81.2%	Any concomitant dose of MTX	83.0%
Concomitant low dose (<10 mg/week) of MTX	5.1%	Concomitant low dose (<15 mg/week) of MTX	12.2%
Concomitant medium dose (≥10 and <15 mg/week) of MTX	19.1%	Concomitant medium dose (≥10 and <15 mg/week) of MTX	40.2%
Concomitant high dose (≥ 15 mg/week) of MTX	75.8%	Concomitant high dose (≥ 15 mg/week) of MTX	47.6%
Any concomitant allowed dose of steroids	63.9%	Any concomitant allowed dose of steroid	71.4%

TJC28: 28 tender joint count; SJC28: 28 swollen joint count; ESR: erythrocyte sedimentation rate; DAS28-ESR: Disease activity score in 28 joints (DAS28)-erythrocyte sedimentation rate (ESR); CRP: C- Reactive protein; DAS28-CRP: disease activity score in 28 joints [DAS28]-C reactive protein [CRP]; HAQ: Health Assessment Questionnaire; sDMARD: synthetic DMARD; MTX: methotrexate.

Statistical analysis

To compare the baseline characteristics and efficacy after 6 months between the Italian and Rest of the World populations the *t*-test was used for all the continuous variables; The Chi squared test was used for all the categorical variables. A limit of these analyses is that they are *post hoc* in nature and many tests were performed without adjustments for multiplicity. Regression analyses have been performed to compare the efficacy results in both the evaluated groups. Nominal *p*-values are provided for all the comparisons. Statistical significance was expressed by a *p*-value <0.05.

Results

Baseline characteristics of patients

Table I shows the baseline characteristics of the Italian patients. The majority of patients were female (79.6%), with a mean age of 55.5 years and we observed a statistical difference with the Rest of the World patients in which a lower age has been reported, 52.2 years (p=0.01). Compared to the Rest of the World population, Italian patients showed a lower mean of number of TJC28 (11.1 *vs*. 13.0, p=0.006), SJC28 (6.5 *vs*. 9.71, p<0.0001), and a lower value of both DAS28-ESR score (5.75 *vs*. 5.97, p=0.045) and DAS28- C reactive protein (CRP) score (5.1 *vs*. 5.4, p=0.0001), respectively. Compared to the Rest of World, Italian subjects had a higher mean ESR at baseline (40.4 mm/hr vs. 34.7 mm/hr, p=0.02).

At baseline, 77.1% of Italian patients had high disease activity and 22.9% of patients had moderate disease activity, as measured by DAS28 scores mirroring the results observed worldwide. In addition, a large percentage of Italian patients showed a significantly short disease duration (≤2 years) when compared to the Rest of the World population (p=0.036).

As far as sDMARD failures were concerned, the majority of Italian patients

Table II. Efficacy results of Italian patients and Rest of the World patients.

Rest of the World results		Italian results	
Percentage (%) of patients EULAR responders	82.1%	Percentage (%) of patients EULAR responders	79.6%
Percentage (%) of patients EULAR DAS28-ESR Low disease activity	37.6%	Percentage (%) of patients EULAR DAS28-ESR Low disease activity	32.7%
Percentage (%) of patients EULAR DAS28-ESR remission	24.1%	Percentage (%) of patients EULAR DAS28-ESR remission	17.3%
Percentage (%) of patients HAQ-DI ≤0.5	37.5%	Percentage (%) of patients HAQ-DI ≤0.5	34.7%

DAS28-ESR: Disease activity score in 28 joints (DAS28)-erythrocyte sedimentation rate (ESR); HAQ: Health Assessment Questionnaire.

received biologic therapy after the failure of the first sDMARD. The analysis of this result, between Italian patients and the Rest of the World study, showed a statistical difference (33.6% *vs*. 60.2%, $p<0.0001$). As consequence, a lower proportion of patients failing 2 and 3 sDMARDs was observed in Italian cohort (36.3% *vs*. 24.5%, $p=0.001$; 30.1% *vs*. 15.3%, $p<0.0001$; respectively). Furthermore, a significant difference in the MTX dosage was observed. Specifically, when we compared Italian patients with the Rest of the World population, we reported a statistical difference in the MTX dosage with high dosages, ≥15 mg/week (47.6% *vs*. 75.8%, $p<0.0001$).

Efficacy results

As shown in Table II, after 6 months of GLM treatment, the results concerning the therapeutic response of the Italian patients did not differ from those observed in the Rest of the World cohort: good/moderate EULAR response 79.6% *vs*. 82.1%, respectively; DAS28-ESR remission 17.3% *vs*. 24.1%, respectively; DAS28-ESR low disease activity 32.7% *vs*. 37.6%, respectively. Furthermore, no difference was observed in the percentage of responders at any scheduled visit between the Italian cohort and the Rest of the World patients. In fact, after 1 month, DAS28-ESR remission in Rest of the World patients *versus*. Italian patients was: 7.7% *vs*. 3.1%, respectively; after 3 months: 16.1% *vs*. 12.2%, respectively; at the end of month 6: 23.9% *vs*. 17.4%, respectively. After 1 month, DAS28-ESR low disease activity in Rest of the World patients *versus* Italian patients was: 16.32% *vs*. 14.29%, respectively; after 3 months: 28.14% *vs*. 22.45%, respectively; at the end of 6 month: 37.44% *vs*. 32.65%, respectively.

To assess the possible differences in clinical response between the 2 groups, we performed a regression analysis, evaluating the percentage of patients reaching the following outcomes, at 6 month: i. EULAR clinical response; ii. low disease activity; iii. clinical remission; iv. HAQ-DI ≤0.5. Our analyses failed to show any significant difference, in the percentage of patients reaching the clinical outcomes, between the 2 groups (Table III). Furthermore, we observed that, in both groups, higher the baseline value of DAS28-ESR, higher the probability to achieve a EULAR clinical response, and, specifically, patients with lower baseline DAS28-ESR values more likely reached the good clinical outcomes: the DAS28-ESR low disease activity, the DAS28-ESR remission and the HAQ-DI ≤0.5.

Safety

Concerning GLM safety profile in the Italian sub-set of the GO-MORE trial, 6% of enrolled Italian patients (n=100) experienced serious adverse events. The pattern of serious adverse events was consistent with previous reports on GLM with no new signals identified.

Patient's evaluation of the autoinjector

Italian patients evaluated the autoinjector device after 3 and 6 months of therapy. More than 90% of patients reported that the overall autoinjection experience was either favourable or extremely favourable, after 3 and 6 months of therapy (95% and 97%, respectively). No pain or mild pain with autoinjector use was reported by more than 90% of patients at the start of month 4 and end of month 6 (95% and 94%, respectively). The pattern of ratings for dis-

Table III. Comparison of the efficacy results between Italian patients and Rest of the World patients by using regression analysis.

Outcome variable at 6 months	Covariates	Odds ratio	95% CI	*p*-value
Percentage (%) of patients EULAR responders	Rest of the World *vs*. Italy	1.160	(0.703, 1.912)	0.561
	DAS28-ESR Baseline	1.082	(0.997, 1.174)	0.058
Percentage (%) of patients EULAR DAS28-ESR Low disease activity	Rest of the World *vs*. Italy	1.451	(0.924, 2.277)	0.106
	DAS28-ESR Baseline	0.514	(0.477, 0.554)	<0.0001
Percentage (%) of patients EULAR DAS28-ESR remission	Rest of the World *vs*. Italy	1.785	(1.028, 3.099)	0.039
	DAS28-ESR Baseline	0.521	(0.480, 0.566)	<0.0001
Percentage (%) of patients HAQ-DI ≤0.5	Rest of the World *vs*. Italy	1.366	(0.846, 2.203)	0.202
	HAQ-DI Baseline	0.206	(0.180, 0.236)	<0.0001

DAS28-ESR: Disease activity score in 28 joints (DAS28)-erythrocyte sedimentation rate (ESR); HAQ: Health Assessment Questionnaire.

comfort upon injection was similar to the pattern for pain ratings, more than 90% of patients after 3 and 6 months of therapy reported no or mild discomfort (93% and 95% respectively). More than 90% of patients found the autoinjector to be easy to use after 3 and 6 months of therapy (95% and 97%, respectively). When we compared these results with the worldwide study, no significant differences were found.

Discussion

The GO-MORE study evaluated the efficacy and safety of subcutaneous GLM, as add-on therapy in patients with active RA, despite sDMARD treatment (13). In the last years, it has been pointed out how trial populations may be heterogeneous for individual patient characteristics such as age, sex, disease severity, comorbidities or access to treatment, despite strict enrolment criteria On these bases, subgroup analyses are common in clinical trials (11, 12) and in this paper, we reported the results concerning the Italian cohort of patients enrolled GO-MORE trial, recruited in different Italian rheumatologic clinical units, the latter ensuring both homogeneous standard of care and strictly adherence to national and international guidelines.

Comparing the baseline characteristic of Italian cohort with the worldwide GO-MORE study, we observed that a larger percentage of Italian patients showed a shorter disease duration. It must be pointed out that RA patients enrolled in this study were classified according to the 1987 ACR criteria. The available literature suggests that patients, classified by using the 2010 ACR/EULAR criteria, may have a less severe disease course (14). In fact, patients fulfilling the 2010 criteria tend to develop a less severe radiological joint damage and to achieve clinical remission more often than patients fulfilling the 1987 criteria (14). In addition, it has been also reported that patients fulfilling 2010 criteria may reach more often the DMARD-free remission and an increased proportion of RA patients, with self-limiting disease, after 2 years of follow-up, was observed (14). These data might fit within the observations that the 2010 classification criteria have a lower specificity than the 1987 criteria and patients fulfilling the 2010 criteria and not the 1987 criteria may represent a milder set of patients (1-3). Interestingly, in the Italian cohort, we analysed RA patients with a relatively early onset of the disease fulfilling the 1987 ACR criteria that, probably are affected by a more severe long-term outcome. It will be of interest, in a long term follow up of the GO-MORE population to evaluate the evaluation of the structural damage, after some years from the beginning of the treatment with GLM. In fact, the Italian subset, with a shorter disease duration, received the biologic treatment earlier than the worldwide population. It is well known that an earlier introduction of TNF inhibitor together with sDMARDs, has been associated with a significant reduction of structural joint damage and earlier treatment have been proven to be more effective than later therapy (3, 4). Furthermore, different studies supported the hypothesis of a drug-signature, and the improvement of structural damage, observed during the trial period, appeared to be maintained and perhaps even continued, independent of subsequent anti-rheumatic therapy, suggesting that an earlier intervention may be more important than the therapeutic choice (15-18).

It must be pointed out that 2/3 of Italian patients were enrolled after the failure of the first sDMARD, mainly MTX. In this context, the results from the QUEST-RA database indicated that treatment-related variables may be recognised between ‘‘higher” gross domestic product and ‘‘lower” gross domestic product countries (18, 19). In fact, countries with lower socioeconomic welfare tend to have stricter eligibility criteria to biologic drugs and the iniquity in access to treatment may influence the long-term outcome in RA patients (7, 8, 18-20). Differently from the Italian cohort, the results of the Rest of the World study showed that the largest percentage of patients failed 2 or more sDMARDs (13), before receiving GLM, confirming that inside a worldwide trial population, not only different therapeutic approaches but also different therapeutic perspectives and related outcomes may be found. Despite of the strict criteria for enrolment and therapies, these differences suggest that some results may be unrelated to the study design but to the different approach in different health national systems (7, 8), supporting the need of a sub-analysis of the published data.

As far as efficacy is concerned, the majority of Italian patients showed a good clinical response to GLM treatment and these results parallel the results obtained in the worldwide GO-MORE population (13) and confirm previous papers about studies RA enrolling patients treated by GLM and TNF inhibitors (21-25). Furthermore, our regression analyses did not show any significant difference between the Italian cohort and the worldwide study in the clinical responses, confirming the efficacy of GLM in our homogeneous subset of patients. Of interest, our results pointed out that, in both the groups, higher the baseline value of DAS28-ESR, higher the probability to achieve a EULAR clinical response, and, of note, patients with lower baseline DAS28-ESR values more likely reached the good clinical outcomes and/or remission, improving their quality of life, as shown by a marked decrease of HAQ-DI.

Recently, an analysis of the GO-MORE study explored factors influencing the evaluations of an autoinjector device, used for subcutaneous injection of GLM, was performed. Two-thirds of patients chose to self-inject with the autoinjector that was generally considered easy to use and reported just little pain or discomfort (26). In the Italian cohort, RA patients were treated by autoinjector device, and in this cohort, the autoinjection experience was considered extremely favourable, easy to use and painless. It is well known, that poor adherence to medication regimens is common and contributes to substantial worsening of disease, death, and increased health care costs (27). Therefore, a better usability of drug and the absence of pain after infusion may influence the adherence of the treatment of RA patients for both sDMARD therapy and biologic drugs (28-30).

In conclusion, the analysis of a homogeneous subset of patients, enrolled in

the Italian GO-MORE study confirms that, despite the strict inclusion criteria, some differences in trial population may be observed concerning the characteristics of the studied patients such as age, disease duration, and access to treatment. In this specific setting, GLM in the Italian patients showed a favourable benefit-to-risk profile. Italian patients reported that the use of the autoinjector device is considered comfortable and largely accepted, probably increasing the retention rate of the drug and adherence to the therapy. Of interest, we observed a strong association between the baseline value of DAS28-ESR and the possibility of the EULAR good clinical response. Further subset analyses in the long follow-up period will provide new data concerning the outcome the patients enrolled worldwide.

Italian GO-MORE Investigators:
[1]Bruno Lagana'
[2]Francesco Versace
[3]Fabrizio Cantini
[4]Roberto Gerli
[5]Walter Grassi
[6]Gianfranco Ferraccioli
[7]Alberto Migliore
[8]Guido Valesini
[9]Giovanni Minisola
[10]Giuseppe Paolazzi
[11]Maria G. Sabbadini
[12]Giovanni Del Sante
[13]Piercarlo Sarzi Puttini
[14]Magda Scarpellini
[15]Raffaele Pellerito
[16]Gerolamo Bianchi
[17]M. Rosa Pozzi
[18]Giovanni Triolo
[19]Daniela Iacono
[20]Rosario Foti
[21]Giuseppe Varcasia
[22]Amato De Paulis
[23]Pier Andrea Rocchetta
[24]Vasiliki Liakouli
[24]Paola Cipriani

[1]U.O.S. Malattie Autoimmuni/U.O.C. Immunologia, Allergologia e Reumatologia, Azienda Ospedaliera "Sant'Andrea", Roma;
[2]S.C di Reumatologia ASL 2 Savonese, Ospedale San Paolo, Genova;
[3]U.O. Medicina II Reumatologia Ospedale "Misericordia e Dolce", Prato; [4]Medicina Interna e Scienze Oncologiche Dipartimento Medicina Clinica e Sperimentale dell' Università degli Studi di Perugia;
[5]Università Politecnica delle Marche Clinica Reumatologica Ospedale Murri Jesi (Ancona);
[6]U.O.C. di Reumatologia Università Cattolica del Sacro Cuore Università Cattolica del Sacro Cuore Policlinico Universitario Agostino Gemelli, Roma;
[7]Dipartimento Medicina – Reumatologia Ospedale Fatebenefratelli San Pietro, Roma;
[8]Clinica e Terapia Medica Università degli Studi "La Sapienza" Azienda Ospedaliera Policlinico Umberto I, Roma;
[9]U.O.C. Reumatologia Ospedale S.Camillo, Roma;
[10]U.O. Reumatologia Presidio Ospedaliero Santa Chiara, Trento;
[11]U.O. di Medicina Generale, Immunologia, Reumatologia e Allergologia IRCCS Fondazione S. Raffaele del Monte Tabor Milano;
[12]Medicina Interna e Reumatologia Azienda Ospedaliera Universitaria di Parma;
[13]Struttura Complessa di Reumatologia Azienda Ospedaliera Luigi Sacco, Milano;
[14]Unità Operativa di Reumatologia Ospedale "G. Fornaroli" di Magenta, Azienda Ospedaliera "Ospedale Civile di Legnano";
[15]Dipartimento Area Medica, S.S. di Reumatologia Azienda Ospedaliera Ordine Mauriziano di Torino;
[16]S.C. Dipartimento di Reumatologia Presidio Ospedaliero Genova Levante;
[17]Dipartimento di Reumatologia Azienda Ospedaliera San Gerardo, Monza;
[18]U.O Reumatologia Dipartimento di Medicina Interna Ospedale Civico P. Giaccone, Palermo;
[19]D.A.I. di Medicina Interna e Specialistica e Sperimentale C.C, Azienda Osp. Universitaria II Università di Napoli;
[20]U.O. Reumatologia Azienda Ospedaliera Universitaria Vittorio Emanuele, Ferrarotto, Santo Bambino, Catania;
[21]U.O. Semplice di Reumatologia Ospedale Civile Minervini, Cosenza;
[22]U.O. S - Dipartimentale di Reumatologia Ospedale "San Giovanni Bosco"Napoli; Immunologia Clinica ed Allergologia Azienda Osp. Univ. Federico II, Napoli;
[23]Struttura Semplice Dipartimentale Reumatologia Azienda Sanitaria Ospedaliera SS. Antonio e Biagio e Cesare Arrigo di Alessandria;
[24]Cattedra di Reumatologia e UO di Immunoreumatologia, Università degli studi dell'Aquila, Ospedale San Salvatore L'Aquila, L'Aquila.

References

1. LINDEN MP, KNEVEL R, HUIZINGA TW, VAN DER HELM-VAN MIL AH: Classification of rheumatoid arthritis: comparison of the 1987 American College of Rheumatology criteria and the 2010 American College of Rheumatology/European League Against Rheumatism criteria. *Arthritis Rheum* 2011; 63: 37-42.
2. HAIR MJ, LEHMAN KA, VAN DE SANDE MG, MAIJER KI, GERLAG DM, TAK PP: The clinical picture of rheumatoid arthritis according to the 2010 American College of Rheumatology/European League Against Rheumatism criteria: is this still the same disease? *Arthritis Rheum* 2012; 64: 389-93.
3. BURGERS LE, VAN NIES JA, HO LY, DE ROOY DP, HUIZINGA TW, VAN DER HELM-VAN MIL AH: Long-term outcome of rheumatoid arthritis defined according to the 2010-classification criteria. *Ann Rheum Dis* 2014; 73: 428-32.
4. SMOLEN JS, ALETAHA D: Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015;11:276-89.
5. PINCUS T, SOKKA T: Should contemporary rheumatoid arthritis clinical trials be more like standard patient care and vice versa? *Ann Rheum Dis* 2004; 63: ii32-ii39.
6. PINCUS T, SOKKA T: Clinical trials in rheumatic diseases: designs and limitations. *Rheum Dis Clin North Am* 2004; 30: 701-24.
7. PUTRIK P, RAMIRO S, KVIEN TK *et al*.: Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis* 2014; 73: 198-206.
8. PUTRIK P, RAMIRO S, KVIEN TK *et al*.: Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? *Ann Rheum Dis* 2014; 73: 2010-21.
9. PINCUS T, SOKKA T, KAUTIAINEN H: Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. *Arthritis Rheum* 2005; 52: 1009-19.
10. JACOBS JW: Lessons for the use of non-biologic anchor treatments for rheumatoid arthritis in the era of biologic therapies. *Rheumatology* (Oxford) 2012; 51 (Suppl. 4): iv27-33.
11. SUN X, BRIEL M, BUSSE JW *et al*.: The influence of study characteristics on reporting of

subgroup analyses in randomised controlled trials: systematic review. *BMJ* 2011; 28; 342:d1569.
12. KASENDA B, SCHANDELMAIER S, SUN X *et al*.: Subgroup analyses in randomised controlled trials: cohort study on trial protocols and journal publications. *BMJ* 2014; 349: g4539.
13. COMBE B, DASGUPTA B, LOUW I *et al*.: 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: 1477-86.
14. BYKERK VP, JAMAL S, BOIRE G *et al*.: The Canadian Early Arthritis Cohort (CATCH): patients with new-onset synovitis meeting the 2010 ACR/EULAR classification criteria but not the 1987 ACR classification criteria present with less severe disease activity. *J Rheumatol* 2012; 39: 2071-80.
15. RANTALAIHO V, KAUTIAINEN H, KORPELA M *et al*.: Targeted treatment with a combination of traditional DMARDs produces excellent clinical and radiographic long-term outcomes in early rheumatoid arthritis regardless of initial infliximab. The 5-year follow-up results of a randomized clinical trial, the NEO-RACotrial. *Ann Rheum Dis* 2014; 73: 1954-61.
16. RANTALAIHO V, KORPELA M, LAASONEN L *et al*.: Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. *Arthritis Res Ther* 2010; 12: R122.
17. VAN TUYL LH, BOERS M, LEMS WF *et al*.: Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 807-12.
18. SOKKA T, KAUTIAINEN H, TOLOZA S *et al*.: QUEST-RA GROUP: QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007; 66: 1491-6.
19. SOKKA T, KAUTIAINEN H, PINCUS T *et al*.: Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST RA database. *Ann Rheum Dis* 2009; 68: 1666-72.
20. GVOZDENOVIĆ E, WOLTERBEEK R, ALLAART CF *et al*.: Assessment of global disease activity in rheumatoid arthritis by patients and physicians: differences across countries in the METEOR database. *J Clin Rheumatol* 2015; 21: 349-54.
21. SANTOS-MORENO P, SÁNCHEZ G, GÓMEZ D, BELLO-GUALTERO J, CASTRO C: Direct comparative effectiveness among 3 anti-tumor necrosis factor biologics in a real-life cohort of patients with rheumatoid arthritis. *J Clin Rheumatol* 2016; 22: 57-62.
22. EMERY P, FLEISCHMANN RM, STRUSBERG I *et al*.: Efficacy and safety of subcutaneous golimumab in methotrexate-naïve patients with rheumatoid arthritis: 5-year results of the GO-BEFORE trial. *Arthritis Care Res* (Hoboken) 2016; 68: 744-52.
23. KEYSTONE EC, GENOVESE MC, HALL S *et al*.: Safety and efficacy of subcutaneous golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: final 5-year results of the GO-FORWARD Trial. *J Rheumatol* 2015; 43: 298-306.
24. BARRA L, HA A, SUN L, FONSECA C, POPE J: Efficacy of biologic agents in improving the Health Assessment Questionnaire (HAQ) score in established and early rheumatoid arthritis: a meta-analysis with indirect comparisons. *Clin Exp Rheumatol* 2014; 32: 333-41.
25. PAPAGORAS C, VOULGARI PV, DROSOS AA: Golimumab, the newest TNF-α blocker, comes of age. *Clin Exp Rheumatol* 2015; 33: 570-7.
26. SCHULZE-KOOPS H, GIACOMELLI R, SAMBORSKI W *et al*.: Factors influencing the patient evaluation of injection experience with the SmartJect autoinjector in rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33: 201-8.
27. OSTERBERG L, BLASCHKE T: Adherence to medication. *N Engl J Med* 2005; 353: 487-97.
28. CIPRIANI P, RUSCITTI P, CARUBBI F, LIAKOULI V, GIACOMELLI R: Methotrexate in rheumatoid arthritis: optimizing therapy among different formulations. Current and emerging paradigms. *Clin Ther* 2014; 36: 427-35.
29. GIACOMELLI R, GORLA R, TROTTA F *et al*.: Quality of life and unmet needs in patients with inflammatory arthropathies: results from the multicentre, observational RAPSODIA study. *Rheumatology* (Oxford) 2015; 54: 792-7.
30. SALAFFI F, CAROTTI M, DI CARLO M, FARAH S, GUTIERREZ M: Adherence to anti-tumor necrosis factor therapy administered subcutaneously and associated factors in patients with rheumatoid arthritis. *J Clin Rheumatol* 2015; 21: 419-25.