Good Clinical Response, Remission, and Predictors of Remission in Rheumatoid Arthritis Patients Treated with Tumor Necrosis Factor-α Blockers: The GISEA Study

LUANA MANCARELLA, FRANCESCA BOBBIO-PALLAVICINI, FULVIA CECCARELLI, PAOLA CHIARA FALAPPONE, ANGELO FERRANTE, DOMENICO MALESCI, ALFONSO MASSARA, FRANCESCA NACCI, MARIA ELENA SECCHI, STEFANIA MANGANELLI, FAUSTO SALAFFI, MARIA LISA BAMBARA, STEFANO BOMBARDIERI, MAURIZIO CUTOLO, CLODOVEO FERRI, MAURO GALEAZZI, ROBERTO GERLI, ROBERTO GIACOMELLI, WALTER GRASSI, GIOVANNI LAPADULA, MARCO MATUCCI CERINIC, CARLOMAURIZIO MONTECUCCO, FRANCESCO TROTTA, GIOVANNI TRIOLO, GABRIELE VALENTINI, GUIDO VALESINI, GIANFRANCO F. FERRACCIOLI, for the GISEA group

ABSTRACT. ***Objective.*** To assess the prevalence of good clinical response and remission in rheumatoid arthritis (RA) patients with longstanding disease treated with anti-tumor necrosis factor-α (TNF-α) drugs at outpatient clinics.

Methods. Retrospective national study of 14 academic tertiary referral rheumatology medical centers. RA patients with a Disease Activity Score (DAS28) > 3.2 were defined as having active disease and could start TNF-α blockers. All patients received one TNF-α blocker plus methotrexate (10–20 mg/wk). At the third month the patients were categorized as responders or nonresponders, based on improvement of at least 0.25 of the Health Assessment Questionnaire (HAQ). Those who had improved by at least 0.25 HAQ were analyzed for possible predictors of DAS28 remission at the sixth month.

Results. A total of 1257 patients started TNF-α blockers. Of these, 591 (46.7%) reached the sixth month with an improvement of HAQ of 0.25 at the third month. In the cohort of patients reaching HAQ of 0.25, DAS28 remission was seen in 24% of rheumatoid factor (RF)-positive and 36% of RF-negative patients ($p = 0.03$). Logistic regression analysis for predictors of remission identified age at baseline, HAQ < 1.63, and RF negativity as positive predictors of remission at 6 months along with sex (male).

Conclusion. We show that only a minority of patients with longstanding RA achieve a good clinical response or remission at the outpatient community level. Predictors of remission identify characteristics commonly observed in subsets with less severe RA. (First Release July 1 2007; J Rheumatol 2007;34:1670–3)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — TUMOR NECROSIS FACTOR-α BLOCKERS
GOOD CLINICAL RESPONSE — DISABILITY SCORE — REMISSION

Clinical trials have convincingly demonstrated the efficacy of tumor necrosis factor-α (TNF-α) blockers in rheumatoid arthritis (RA). Recent data from our national registry have shown that a good clinical response and remission are much rarer than shown in randomized controlled clinical trials (RCT)[1] and the most likely interpretation is that exclusion criteria could seriously influence not only the safety issue in general, but also the final clinical outcomes in aggressive and severe disease at the community level.

We report the analysis of good responses defined accord-

From the Division of Rheumatology, Catholic University of the Sacred Heart, Rome; and Rheumatic Disease Units, Universities of Verona, Genova, Modena, Siena, Perugia, Ancona, Bari, Pavia, Firenze, Palermo, Ferrara, Napoli 2, and Rome–La Sapienza, Italy.

Supported by Gruppo Italiano Studio Early Arthritis (Italian Study Group for Early Arthritis).

L. Mancarella, MD; G.F. Ferraccioli, MD, Professor of Rheumatology, Division of Rheumatology, Catholic University of the Sacred Heart; F. Bobbio-Pallavicini, MD; C. Montecucco, MD, Professor, Rheumatic Disease Unit, IRCCS, University of Pavia; F. Ceccarelli, MD; G. Valesini, MD, Professor, Rheumatic Disease Unit, University of Rome-La Sapienza; P.C. Falappone, MD; G. Lapadula, Professor, MD, Rheumatic Disease Unit, University of Bari; A. Ferrante, MD; G. Triolo, MD, Professor, Rheumatic Disease Unit, University of Palermo; D. Malesci, MD; G. Valentini, MD, Professor, Rheumatic Disease Unit, University of Napoli 2; A. Massara, MD; F. Trotta, MD, Professor, Rheumatic Disease Unit, University of Ferrara; F. Nacci, MD; M. Matucci Cerinic, MD, Professor, Rheumatic Disease Unit, University of Firenze; M.E. Secchi, MD; M. Cutolo, MD, Professor, Rheumatic Disease Unit, University of Genova; S. Manganelli, MD; M. Galeazzi, MD, Professor, Rheumatic Disease Unit, University of Siena; F. Salaffi, MD; W. Grassi, MD, Professor, Rheumatic Disease Unit, University of Ancona; M.L. Bambara, MD, Professor, Rheumatic Disease Unit, University of Verona; S. Bombardieri, MD, Professor; C. Ferri, MD, Rheumatic Disease Unit, University of Modena; R. Gerli, MD, Professor, Rheumatic Disease Unit, University of Perugia; R. Giacomelli, MD, Professor.

Address reprint requests to Dr. G.F. Ferraccioli, Catholic University of the Sacred Heart, Association Columbus, Via Moscati 31, 00168, Rome, Italy. E-mail:gf.ferraccioli@rm.unicatt.it

Accepted for publication March 24, 2007.

ing to European League Against Rheumatism (EULAR) criteria and the predictors of remission in a cohort of patients with RA treated with TNF-α blockers at a community level. Our aim was to analyze the percentage of good EULAR response and of remissions, calculated using Disease Activity Score (DAS) values, and the predictors of remission in patients who had a clinically meaningful response after at least 6 months of treatment with a TNF-α blocker.

MATERIALS AND METHODS

Patients. All the analyzed patients were enrolled at tertiary referral medical centers (university hospitals) and followed at the community clinics of the rheumatology units of 14 university medical centers spread over the whole country. The study was retrospective and reflects the common practice of using anti-TNF-α drugs at the community level. The criterion to receive TNF-α blockers was active RA disease with a Disease Activity Score (DAS28) > 3.2[3-5] despite treatment with conventional disease modifying antirheumatic drugs (DMARD) alone or in combination. All patients in RCT at the different centers and all patients with a DAS of low disease activity were excluded. All the recruited patients had regular followups (monthly or bimonthly assessments) over the next 6 months, in which clinical data [pain, swollen and tender joint counts, Health Assessment Questionnaire (HAQ), patient and physician global assessments, sex, age, age at onset, disease duration)] and laboratory measures [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF)], and all the safety hematology and biochemical measures, were obtained. Infliximab was given to 27%, etanercept to 49%, and adalimumab to 24% of the patients. All patients who presented adverse reactions or who missed the followup examinations (poor compliance) were excluded from the analysis. The Italian guidelines suggest that once a 3-month trial does not result in a clinically meaningful improvement, treatment with the biologic drug should be stopped. Some patients were switched to another biologic drug (one study has already been published[6]), some continued combination of DMARD, and some entered other trials.

Study protocol. At study start we decided that in order to obtain the strongest information on predictors of remission, we should have the whole cohort analyzed for efficacy and safety; and only those reaching at least a clinically meaningful response on HAQ, which according to the literature can be between 0.2 and 0.3, should be analyzed for possible predictors of remission. We selected 0.25 as the cutoff value[4]. During the study all the patients that did not achieve HAQ improvement at the third month were not examined further for predictors of response. A good EULAR response and remission were defined on the basis of the DAS score; a low disability score of HAQ at < 0.5 was also used to define the patients achieving disability remission or not[6,7].

Statistical analysis. The statistical analysis was carried out using the SPSS program (SPSS, Chicago, IL, USA). Means, standard deviations, and differences among the means between groups were analyzed by Wilcoxon and Mann-Whitney tests for unpaired data. Categorical variables were analyzed using chi-square test or Fisher's test, depending on sample size restrictions, and the odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. A multiple logistic regression using SPSS 11.0 was employed to detect the influence on the dependent variable on remission and good-health status by the independent variables that reached the value of $p < 0.25$ at the univariate analysis. The values are expressed as OR (95% CI). The diagnostic values of the clinical variables were assessed considering the mean values for some variables (age, age at onset, disease duration, tender joint count, swollen joint count, HAQ) or the normal values (ESR < 28 mm/h, CRP < 5 mg/l, RF < 20 IU/ml) as cutoff points. The analysis normalized the results as a function of the intake, or not, of steroids. We used a stepwise backward-elimination procedure, following the method suggested by Hosmer and Lemeshow. The chi-square test and the Hosmer-Lemeshow test were used to assess the fitting of the model. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Of 1257 patients with longstanding RA starting TNF-α blocker therapy, only 682 reached the sixth month (54.25%). The others dropped out because of lack of efficacy or side effects. More particularly, 32% did not obtain significant clinical benefits and dropped out because of inefficacy; 14% had adverse events (8% skin reactions, 2% infusion reactions, 4% others: infections, hematologic, hepatic, gastrointestinal) and decided not to continue. Of the 682, 91, despite achieving the 0.25 HAQ improvement, could not be carefully assessed over time in terms of total clinical and laboratory variables and therefore were excluded. Given the entry criteria, when comparing the clinical and laboratory measures of the excluded cohort versus those of the studied cohort, the only slight difference was in the percentage of patients taking steroids (54% vs 49%). Five hundred ninety-one (46.75% of the whole cohort) had regular bimonthly assessments of clinical and laboratory measures and at least a 0.25 improvement in the HAQ score (Table 1). This was the cohort that we decided to analyze further. In this cohort the female:male ratio was 2.16 (404:187), mean age was 53.3 ± 12.7 years, and mean HAQ score at baseline was 1.63 (± 0.6). At baseline 467 were RF-positive and 124 were RF-negative (Table 1). Among the RF-positive and RF-negative, DAS28 < 2.6 was reached in 24% and 36%, respectively ($p = 0.03$), and a good EULAR response was seen in 37% versus 50%, respectively ($p = 0.01$) (Table 2). We then analyzed more closely the cohort of 591 patients who during the first 3 months achieved HAQ improvement of at least 0.25, to identify the predictors of remission. Overall, 61 men (32%) and 97 women (24%) achieved remission and the difference between sexes was statistically significant ($p = 0.032$). The mean values of the variables were taken as cutoff values in the logistic regression analysis: age (53 yrs), age at disease onset (41.5 yrs), sex, disease duration (12 yrs), RF test (positive or nega-

Table 1. Characteristics of 591 patients with rheumatoid arthritis at baseline.

Variables	
Women (%)	404 (67)
Age (yrs)	53.3 ± 12.7
Age at diagnosis (yrs)	41.5 ± 13.7
Duration of disease (yrs)	11.6 ± 7.6
Swollen joints (n)	10.4 ± 7.1
Tender joints (n)	17.1 ± 9.4
HAQ score	1.625 ± 0.661
DAS28	5.9 ± 1.2
ESR (mm/h)	41.2 ± 25.0
Patients taking steroids	49%
(median mg, range)	5 (1–7.5)
C-reactive protein positivity*	72.4 %
RF positivity (% patients)**	79%

* CRP > 5 mg/l; ** RF > 20 IU/ml. HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor.

Table 2. Characteristics of patients with rheumatoid arthritis at baseline.

Variables	RF Positivity (n = 467)	RF Negativity (n = 124)	p
Sex, % women	66	70	
Age (yrs)	53.6 ± 12.9	53.1 ± 12.8	0.63
Age at diagnosis (yrs)	41.8 ± 13.5	41.1 ± 15.0	0.73
Duration of disease (yrs)	11.8 ± 7.5	12.0 ± 8.1	0.87
Swollen joints (n)	10.6 ± 7.4	9.3 ± 6.1	0.15
Tender joints (n)	17.4 ± 9.5	15.4 ± 8.8	0.05
HAQ score	1.7 ± 0.7	1.5 ± 0.6	0.04
DAS28	6.0 ± 1.2	5.7 ± 1.1	0.02
ESR (mm/h)	41.5 ± 4.5	39.9 ± 7.2	0.40
C-reactive protein (mg/l)	22.6 ± 24.8*	19.6 ± 22.9	0.06

For abbreviations, see Table 1.

Table 3. EULAR response according to DAS28 < 2.6 at the sixth month followup.

EULAR Response	RF-Positive Patients*, n (%)	RF-Negative Patients, n (%)	p
Good	164 (37)	60 (50)	0.01
Moderate	241 (54)	45 (37)	0.001
Remission	112 (24)	43 (36)	0.03

EULAR: European League Against Rheumatism.

Table 4. Significance of the various factors predictive of remission (DAS28 < 2.6) at univariate analysis.

Baseline Variables	p*	Univariate Analysis, OR (95% CI)
Sex	0.032	0.659 (0.450–0.965)
Age (≥ 53 yrs)	0.017	0.584 (0.334–0.899)
Age at diagnosis (≥ 41.5 yrs)	0.659	0.794 (0.288–2.189)
Duration of disease (≥ 12 yrs)	0.577	1.112 (0.767–1.612)
Swollen joint count (≥ 10)	0.820	1.037 (0.714–1.507)
Tender joint count (≥ 17)	0.848	1.043 (0.723–1.507)
HAQ score (≥ 1.63)	0.001	0.537 (0.370–0.779)
RF (positivity)	0.025	0.612 (0.398–0.940)
C-reactive protein (≥ 5 mg/l)	0.141	1.378 (0.899–2.110)

* Significance calculated using the chi-squared test.

Table 5. Stepwise logistic regression analysis of predictive factors of remission at baseline.

Baseline Variables	OR (95% CI)
Age (≥ 53 yrs)	0.64 (0.44–0.94)
HAQ score (≥ 1.63)	0.56 (0.38–0.83)
RF (positivity)	0.61 (0.39–0.96)

Hosmer-Lemeshow test: p = 0.935. Hosmer-Lemeshow test: p = 0.554.

tive), swollen joint count (n = 10), tender joint count (n = 17), and HAQ (= 1.63), while for CRP we only considered whether it was positive or negative (Table 4). These were the components of the logistic regression model for remission according to the DAS28 value. The best independent predictors of remission were sex (male), age of the patient < 53 yrs (OR 0.6, 95% CI 0.4–0.90), RF negativity (OR 0.6, 95% CI 0.4–0.96), HAQ < 1.63 (OR 0.5, 95% CI 0.38–0.8) at baseline (Table 5). Finally, we analyzed the percentage of patients achieving a low disability score, defined as HAQ < 0.5: it was achieved in 282 patients (48% of the cohort of 591) and among these 45.4% were RF-positive and 58.1% were RF-negative (p = not significant).

DISCUSSION

The most important finding of this dataset analysis is that the percentage of patients who continued their therapy up to the sixth month was < 60% and that DAS remission was much lower than previously reported in RCT[8,9]. Recently, the Cochin dataset has shown that 64% of their patients (RA and spondyloarthropathies) continued their treatment at 1 year, with RA patients responding less well than spondyloarthritis patients[10]. Of potential interest, however, is the fact that even at the outpatient clinics (which can be considered community level in our country), despite being tertiary referral centers because of the direct access from general physicians, half the patients reached a clinically meaningful result as defined by a HAQ improvement of 0.25. Therefore patients in clinical practice are not representative of those recruited in clinical trials and certainly do not reach the outcomes that have been provided in RCT[11,12]. Among these, remission was observed in a small percentage of patients with a long disease duration.

The most important bias of our study is that we lost a high percentage of patients starting TNF-α blockers, and for this reason decided to analyze possible predictors only considering the cohort of patients that had achieved at least a clinically meaningful response in the first period of treatment. Since the percentage of remission is generally low at the community level, patients who do not achieve at least the lowest clinically meaningful result would certainly confound the identification of predictors. Given that patients should have achieved at least a clinical benefit, the profile of the best responder was quite clear. This profile may be of help in clinical practice, and certainly it identifies patients with a low severity profile. Even more important when looking at the best predictors of remission at baseline, we could identify age at baseline (< 53 yrs), baseline HAQ (< 1.63), and RF negativity as possible identifiers of the best responder. From our results it seems that male patients with RA seem to benefit more from anti-TNF-α strategies than do female patients[13].

A very similar percentage of remission was seen and a low DAS arose as the best predictor of remission in the RABBIT registry along with a HAQ score < 1.75, but in the German registry a higher age reduced the chance of remission[14].

Recently, Hyrich, *et al*[1], considering all the patients in the British Society for Rheumatology Biologic Registry, reported that a higher baseline HAQ score correlated with a lower response rate, but none of the common variables (age, disease duration, RF, previous DMARD use) could identify predictors of future remission.

The results of our analysis at first appear pleonastic: the less aggressive disease responds better than the more aggressive disease. Since it has never been stated, the conclusion should be that even though it is very likely that patients who start with the highest DAS will achieve more in terms of absolute benefit, to achieve remission the baseline values need to be of the less aggressive phenotype. A prospective study employing the algorithm we provided should allow us to define whether we can *a priori* identify the patients who will fully benefit from TNF-α blockers, thus saving healthcare budgets, in terms of regaining working capacity and function. Overall, the results in terms of full control of the disease at the outpatient clinic/community level still remain unsatisfactory[15].

REFERENCES

1. Hyrich KL, Watson KD, Silman AJ, Symmons DPM, and the BSR Biologic Registry. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologic Registry. Rheumatology Oxford 2006;45:1558-65.
2. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
3. Welsing PM, Landewe RB, van Riel PL, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-93.
4. Welsing PM, Borm GF, Van Riel PLCM. Minimal clinically important difference in radiological progression of joint damage. A definition based on patient perspectives. J Rheumatol 2006;33:501-7.
5. Fransen J, Creemers MCW, van Riel PLCM. Remission in rheumatoid arthritis: agreement of the Disease Activity Score (DAS28) with the ARA preliminary remission criteria. Rheumatology Oxford 2004;43:1252-5.
6. Iannone F, Trotta F, Monteccuco C, et al. Etanercept maintains the clinical benefit achieved by infliximab in patients with rheumatoid arthritis who discontinued infliximab because of side effects. Ann Rheum Dis 2007;66:249-52.
7. Wells GA, Boers M, Shea B, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016-24.
8. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381-90.
9. Van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54:1063-74.
10. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor alpha blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33:2433-9.
11. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. Osteoporosis Int 2000;11:533-6.
12. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a trial effect. J Clin Epidemiol 2001;54:217-24.
13. Kvien TR, Uhlig T, Odegard S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: The sex ratio. Ann NY Acad Sci 2006;1069:212-22.
14. Listing J, Stragfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low — results from RABBIT, the German biologic register. Arthritis Res Ther 2006;8:R66.
15. Sesin CA, Bingham CO 3rd. Remission in rheumatoid arthritis: wishful thinking or clinical reality? Semin Arthitis Rheum 2005;35:185-96.