Six and 12 Weeks Treatment Response Predicts Continuation of Tumor Necrosis Factor Blockade in Rheumatoid Arthritis: An Observational Cohort Study from Southern Sweden

ANDERS GÜLFE, LARS ERIK KRISTENSEN, and PIERRE GEBOREK

ABSTRACT. ***Objective.*** To investigate if treatment response predicts continuation of anti-tumor necrosis factor (TNF) treatment in patients with rheumatoid arthritis (RA).

Methods. We investigated if treatment response and/or achieving a certain activity state at 6 weeks or 3 months predicts continuation of treatment in an observational cohort of 1789 anti-TNF-naive patients with established RA disease from southern Sweden.

Results. Response to treatment at 6 weeks at overall/American College of Rheumatology (ACR20) or good/major level (except ACR70) significantly predicted drug continuation. Response according to all criteria sets at overall/ACR20 and at good/major/ACR70 level predicted drug continuation at 3 months, as did achieving low disease activity at 3 months irrespective of activity index applied. Remaining in a high disease activity state predicted drug discontinuation at both timepoints and according to all criteria sets.

Conclusion. Response criteria may be useful aids in deciding on continuation of TNF blockade in RA as early as after 6 weeks of treatment. The various criteria sets perform similarly. (First Release Jan 15 2009; J Rheumatol 2009;36:517-21; doi:10.3899/jrheum.080509)

Key Indexing Terms:
OBSERVATIONAL STUDY — RHEUMATOID ARTHRITIS
ANTI-TUMOR NECROSIS FACTOR TREATMENT — TREATMENT CONTINUATION
PREDICTORS — RESPONSE — DISEASE ACTIVITY STATES

Previously, baseline characteristics have been found to only weakly predict continuation of anti-tumor necrosis factor (TNF) treatment in patients with rheumatoid arthritis (RA)[1,2]. Even though amelioration of symptoms appears to occur early (within weeks) after starting TNF blockade in responding patients with RA, there is a paucity of data regarding the timepoint best suited for deciding on the continuation or stopping of treatment. On the individual level, no rigid guidelines can be given in this regard, but predictors of drug continuation at the group level will give a notion of the (minimal) time needed to judge the meaningfulness of going on with therapy. To address this, we conducted a study of an observational cohort of patients with established RA starting their first course of adalimumab, etanercept, or infliximab. The aim was to investigate whether treatment response or achieving a certain disease activity state at 6 weeks or 3 months predicted continuation of anti-TNF therapy. We also wanted to study whether any specific criteria set was superior in this aim.

From the Department of Rheumatology, Lund University Hospital, Lund, Sweden.

Supported by grants from the Österlund and Kock Foundations, King Gustav V 80 year Fund, Region Skåne, Lund University Hospital, and Reumatikerförbundet.

A. Gülfe, MD; L.E. Kristensen, MD, PhD; P. Geborek, MD, PhD, Lund University Hospital.

Address reprint requests to Dr. A. Gülfe, Department of Rheumatology, Lund University Hospital, SE-221 85 Lund, Sweden.
E-mail: anders.gulfe@med.lu.se

Accepted for publication October 6, 2008.

MATERIALS AND METHODS

Patients with RA and other arthritides who start treatment with TNF blockers and other biologics in southern Sweden are entered into a database maintained by the South Swedish Arthritis Treatment Group (SSATG) as described[3]. The catchment area has a population of about 1.3 million, and the coverage as compared to the sales of the relevant drugs through the pharmacies is 95%[4]. Because of the safety surveillance character of the registry, no ethics committee approval was needed.

Patients eligible for the study had a diagnosis of RA, as judged by the treating rheumatologist, and started their first course of treatment with infliximab, etanercept, or adalimumab from March 1999 through December 2006.

Patients were enrolled continuously. The 3 TNF blockers were studied together, since they have been shown to perform similarly in our cohort[2].

Fulfilment of American College of Rheumatology (ACR) 20%, 50% and 70% response[5]; European League Against Rheumatism (EULAR) overall (moderate + good), moderate, and good response according to original and modified cutoff values[6]; and overall (minor + major), minor, and major response according to the Simple Disease Activity Index (SDAI)[7] and the Clinical Disease Activity Index (CDAI)[8] were calculated at 6 weeks and 3 months. Achievement of low, moderate, or high disease activity

according to the Disease Activity Score in 28 joints (DAS28) original and modified cutoff values[9,10], SDAI[10], and CDAI[11] were also calculated at the same timepoints. Hazard ratios (HR) for stopping treatment were then calculated together with their 95% confidence intervals (CI) and p values for each of the criteria.

Completer analysis was used for response rates at 6 weeks and 3 months due to the limited followup time and observational design of the study. The proportion of patients remaining on therapy at 6 and 12 weeks was estimated using Kaplan-Meier statistics. Drug adherence and discontinuation (due to failure or adverse event) was estimated by life-table analysis with stop date December 2006. Missing data were requested from treating physicians yearly. Cox regression analysis was employed to study predictors of treatment continuation. The regression models included correction for age, disease duration, baseline Health Assessment Questionnaire (HAQ) score[12], baseline C-reactive protein (CRP) level, and concomitant methotrexate use, since all these variables have previously been shown to influence 3-month treatment response[2]. Due to colinearity, a regression model was computed for each of the response criteria and disease activity states studied. P values less than 0.05 were considered significant.

RESULTS

There were 1789 patients with established RA meeting the eligibility criteria, 77% of whom were female. As reporting at 6 weeks in the SSATG system is optional, there were considerably fewer patients with data at 6 weeks than at 3 months. At baseline, mean (standard deviation) age was 56.9 (13.4) years and disease duration 12.1 (10.2) years, number of ongoing disease modifying antirheumatic drugs (DMARD) 0.9 (0.6), HAQ score 1.3 (0.6), DAS28 score 5.5 (1.2), erythrocyte sedimentation rate 35.6 (24.7) mm/h, and CRP 30.8 (33.0) g/l. There were few early withdrawals, with 96% and 94% of patients remaining on therapy at 6 weeks and 3 months, respectively.

The proportions of patients meeting the various response criteria and disease activity stages are given in Table 1. At the lowest level (ACR20, EULAR overall original and modified cutpoints, SDAI overall, and CDAI overall) response rates at 6 weeks were 56%–75%. At 3 months the corresponding rates were 61%–80%. The higher response level (ACR50, EULAR good, SDAI and CDAI major) was achieved by 29%–44% at 6 weeks and 34%–57% at 3 months.

Drug continuation was predicted significantly by achieving ACR20 and ACR50 responses at 6 weeks and all levels of ACR response at 3 months. Similarly, achieving EULAR overall or good responses, both original and modified, predicted continuation of treatment at both timepoints, and this was also true for SDAI and CDAI overall and major. Isolated moderate/minor response did not predict drug continuation for any of the criteria sets at any timepoint (Table 2).

To assess the effect of reason for discontinuation of therapy, the HR for stopping treatment for the strongest predicting variable, the EULAR original overall response, were calculated separately for adverse events and failure. At 6 weeks, the HR for stopping treatment due to adverse events was 1.17 (95% CI 0.61–2.26, p = 0.64), and for failure it was 0.43 (95% CI 0.24–0.76, p = 0.004). The corresponding values at 3 months were 0.44 (95% CI 0.31–0.63, p < 0.0001) and 0.28 (95% CI 0.19–0.41, p < 0.0001), respectively.

Table 1. Response and achievement of disease states according to various criteria. Total n = 1789.

	6 Weeks		3 Months	
	%	Valid n	%	Valid n
Response criteria				
ACR				
ACR20	55	536	61	1234
ACR50	29	536	38	1234
ACR70	8.5	542	14	1234
EULAR original				
Overall	73	499	76	1163
Moderate	45	505	42	1163
Good	29	499	34	1163
EULAR modified				
Overall	69	499	72	1163
Moderate	25	505	18	1163
Good	44	499	54	1163
SDAI				
Overall	75	512	80	1184
Minor	37	518	28	1184
Major	39	512	52	1184
CDAI				
Overall	74	523	79	1195
Minor	30	529	22	1195
Major	43	523	57	1195
Disease stages				
EULAR original				
Remission	18	524	23	1214
Low	35	518	38	1214
Moderate	47	518	46	1214
High	18	518	17	1214
EULAR modified				
Remission	12	524	18	1214
Low	46	518	49	1214
Moderate	41	518	38	1214
High	13	518	12	1214
SDAI				
Remission	4.1	534	8.3	1224
Low	35	528	42	1224
Moderate	20	528	41	1224
High	18	528	17	1224
CDAI				
Remission	4.5	539	8.0	1232
Low	36	533	45	1232
Moderate	44	533	39	1232
High	20	533	19	1232

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; SDAI: Simple Disease Activity Index; CDAI: Clinical Disease Activity Index.

There were 396 patients with complete data at 6 weeks and 3 months. For these patients, the mean HR for the EULAR original overall response to predict discontinuation of therapy was 0.80 (95% CI 0.51–1.25, p = 0.32) at 6 weeks and 0.44 (95% CI 0.29–0.66, p < 0.0001) at 3 months.

Not surprisingly, achieving remission or low disease activity state generally predicts continuation of treatment, especially at 3 months. At 6 weeks, achieving disease remis-

Table 2. Hazard ratios (HR) for stopping tumor-necrosis factor blockade for patients achieving defined response or disease states according to various criteria. Total n = 1789.

	6 Weeks			3 Months		
	HR (95% CI)	p	Valid n	HR (95% CI)	p	Valid n
Response criteria						
ACR						
ACR20	0.55 (0.43–0.71)	< 0.001	526	0.56 (0.47–0.66)	< 0.001	1208
ACR50	0.64 (0.48–0.85)	0.002	526	0.55 (0.46–0.66)	< 0.001	1208
ACR70	1.06 (0.59–1.90)	0.850	526	0.56 (0.42–0.75)	< 0.001	1208
EULAR original						
Overall	0.59 (0.44–0.77)	< 0.001	493	0.47 (0.39–0.56)	< 0.001	1151
Moderate	0.95 (0.66–1.34)	0.763	493	0.87 (0.73–1.04)	0.123	1151
Good	0.72 (0.53–0.97)	0.032	493	0.58 (0.47–0.71)	< 0.001	1151
EULAR modified						
Overall	0.63 (0.48–0.83)	0.001	493	0.48 (0.40–0.57)	< 0.001	1151
Moderate	1.03 (0.69–1.53)	0.895	493	0.96 (0.77–1.19)	0.695	1151
Good	0.61 (0.49–0.79)	< 0.001	493	0.56 (0.47–0.67)	< 0.001	1151
SDAI						
Overall	0.62 (0.45–0.81)	0.001	512	0.47 (0.39–0.57)	< 0.001	1179
Minor	0.80 (0.56–1.15)	0.229	512	1.06 (0.87–1.28)	0.557	1179
Major	0.65 (0.50–0.86)	0.002	512	0.58 (0.48–0.69)	< 0.001	1179
CDAI						
Overall	0.75 (0.57–0.99)	0.044	517	0.53 (0.44–0.65)	< 0.001	1181
Minor	0.94 (0.64–1.37)	0.742	517	1.20 (0.99–1.47)	0.067	1181
Major	0.69 (0.54–0.90)	0.005	517	0.57 (0.48–0.68)	< 0.001	1181
Disease states						
EULAR original						
Remission	1.03 (0.65–1.62)	0.911	502	0.65 (0.51–0.82)	< 0.001	1173
Low	0.69 (0.52–0.93)	0.015	502	0.60 (0.49–0.72)	< 0.001	1173
Moderate	1.04 (0.81–1.34)	0.769	502	0.98 (0.83–1.16)	0.803	1173
High	1.60 (1.15–2.23)	0.005	502	2.18 (1.78–2.69)	< 0.001	1173
EULAR modified						
Remission	1.33 (0.82–2.16)	0.242	502	0.65 (0.50–0.85)	0.001	1173
Low	0.60 (0.45–0.79)	< 0.001	502	0.61 (0.50–0.73)	< 0.001	1173
Moderate	1.24 (0.96–1.60)	0.108	502	1.08 (0.91–1.29)	0.386	1173
High	1.86 (1.28–2.69)	0.001	502	2.15 (1.72–2.69)	< 0.001	1173
SDAI						
Remission	1.85 (0.86–4.02)	0.118	512	0.60 (0.41–0.87)	0.006	1182
Low	0.81 (0.62–1.06)	0.125	512	0.67 (0.56–0.81)	< 0.001	1182
Moderate	0.90 (0.70–1.15)	0.389	512	0.90 (0.76–1.07)	0.224	1182
High	1.73 (1.26–2.39)	0.001	512	2.19 (1.79–2.68)	< 0.001	1182
CDAI						
Remission	1.82 (0.84–3.945)	0.129	517	0.64 (0.441–0.918)	0.016	1189
Low	0.84 (0.64–1.10)	0.192	517	0.70 (0.58–0.84)	< 0.001	1189
Moderate	0.87 (0.68–1.12)	0.237	517	0.84 (0.70–1.00)	0.048	1189
High	1.62 (1.20–2.19)	0.002	517	2.24 (1.84–2.73)	< 0.001	1189

sion according to all criteria does not significantly predict continuation, nor does moderate activity. Remaining in high disease activity state strongly predicts discontinuation of drug irrespective of activity index (Table 2).

Independent of treatment response and disease activity, significant predictors of premature treatment termination by unadjusted Cox regression analysis were: higher age (HR 1.01, 95% CI 1.00–1.01), higher HAQ score (HR 1.21, 95% CI 1.07–1.36), and no methotrexate at inclusion (HR 0.75, 95% CI 0.65–0.87). When adjusting for the strongest predicting response criterion, the EULAR overall original at 3 months, HAQ (HR 1.26, 95% CI 1.09–1.46) and no methotrexate (HR 0.80, 95% CI 0.67–0.96) at inclusion predicted termination of treatment.

Sex, year of treatment initiation, and disease duration prior to treatment initiation did not predict continuation of therapy.

DISCUSSION

The main finding of our observational study of 1789 patients from southern Sweden with longstanding RA is that the key predictors for continuation of anti-TNF treatment were response and achievement of a state of low disease activity, in most instances already after 6 weeks, and very signifi-

cantly after 3 months (Table 2). Conversely, remaining in a high disease activity state strongly predicts drug discontinuation (Table 2). On the other hand, baseline characteristics, although significant, predict treatment continuation only to a lesser degree.

It seems that relatively little change in overall treatment response takes place between the timepoints (Table 1). This is also true for the achievement of disease states (Table 1). There is, however, a clear increase in the proportion reaching a higher degree of response irrespective of criteria set used at 3 months compared to 6 weeks. The modest response rates are not surprising in a cohort of RA patients with mean disease duration of 12 years, having failed at least 2 previous DMARD.

At 6 weeks, continuation of treatment is significantly predicted by response according to ACR20 and ACR50 and EULAR overall and good original and modified, SDAI overall and major, and CDAI overall and major responses (Table 2). ACR70 fails to predict drug continuation at 6 weeks, presumably because of the small number of responders according to this strict criterion. These findings prevail and are even stronger at 3 months, when responses at all ACR levels, and according to all other criteria sets at overall and good/major levels, significantly predict continuation of treatment. By contrast, isolated moderate/minor responses fail to predict drug continuation. Conceivably, the ability of the ACR20 and overall-level responses to significantly predict drug continuation may be due to the good/major components of these merged measures.

As for disease activity states, achieving remission or low disease activity at 3 months predicts drug continuation according to all criteria sets (Table 2). The picture at 6 weeks is less clear, with the DAS28-based criteria for low activity reaching significance, unlike the stricter SDAI and CDAI. Remaining in a high disease activity state strongly predicts drug discontinuation, both at 6 weeks and 3 months, and according to all criteria sets.

Discontinuation of treatment is also independently predicted by the baseline variables higher age and HAQ and no concomitant methotrexate. However, the absolute HR of these predictors are so small that the clinical significance is minor compared to that of response to treatment.

In our study, it thus seems that major response to treatment at 6 weeks in most cases predicts treatment continuation, and this is even clearer at 3 months, applying completer analysis. The same tendency is noted for achieving low disease activity, but this is clearly evident only at 3 months. For patients with complete data at both timepoints, the strongest predicting variable, the EULAR original overall response, significantly predicted drug continuation at 3 months only, illustrating the tendency for completer analysis to inflate results and thus somewhat weakening our conclusions regarding 6-week prediction. However, the failure to predict drug continuation at 6 weeks may be due to lack of power, the number of patients being much lower than in the completer analysis.

As for the reason for treatment termination, there were significant HR for treatment failure at both timepoints and for adverse event at 3 months for the EULAR original overall. It must be remembered that the reason for termination was determined by the treating rheumatologist. Stopping due to treatment failure or adverse event should thus be interpreted with caution, and more emphasis given to the overall reason for stopping treatment[13,14].

Response criteria are intended for comparing treatments in clinical trials, and they have been shown to perform poorly at the individual level in the clinical setting[15]. Interestingly, in this observational, nonrandomized cohort, at the group level, they appear to be the most sensitive predictors of continuation with TNF blockade already after 6 weeks, rather than the achievement of low disease activity. After 3 months, more patients are in a low disease activity state or even remission, and this predicts continuation at this timepoint, but response criteria remain better predictors. Treatment failure, i.e., ongoing high disease activity, predicts stopping of anti-TNF treatment both at 6 weeks and at 3 months. This is not surprising, since it is in accord with the current Swedish guidelines[16]. In early RA trials, rapid suppression of disease activity has been shown to predict low disease activity later[17,18]. This is compatible with our findings in longstanding RA.

The various criteria sets perform similarly and seem to be useful tools aiding a decision on continuation of anti-TNF treatment. One criterion set could hardly be considered superior to another, but the simplicity of the CDAI, which requires no laboratory measure, would make this set especially suited for day to day clinical use. However, activity indexes and response criteria cannot be solely depended upon in making treatment decisions. They do not cover all the dynamic aspects of the disease, and clinical judgment will remain important in the daily care of patients with RA. Indeed, treatment continuation based on the judgment of the treating rheumatologist was the standard by which efficacy was determined in our study. This may be regarded as a surrogate measure, but the prognostication of treatment response by the use of various biomarkers has so far turned out to be difficult[19]. However, the employment of composite measures of disease activity and response to treatment seems to be useful in predicting continuation of treatment as early as 6 weeks after initiation of TNF blockade, at least at the group level. Consequently, decision-making regarding continuation of TNF blockade might be considered as early as at 6 weeks of followup, as opposed to previous guidelines. Thus our finding raises important questions regarding clinical decision-making as well as health economic issues. Even so, our results should be verified in other patient studies.

ACKNOWLEDGMENT

We are indebted to all colleagues and staff in the South Swedish Arthritis Treatment Group for cooperation and data supply, and to Jan-Åke Nilsson for help with statistical calculations.

REFERENCES

1. Hyrich KL, Watson KD, Silman AJ, Symmons DP. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology Oxford 2006;45:1558-65.
2. Kristensen LE, Kapetanovic MC, Gulfe A, Soderlin M, Saxne T, Geborek P. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology Oxford 2008;47:495-9.
3. Geborek P, Saxne T. Clinical protocol for monitoring of targeted therapies in rheumatoid arthritis. Rheumatology Oxford 2000;39:1159-61.
4. Geborek P, Nitelius E, Noltorp S, et al. Population based studies of biological antirheumatic drug use in southern Sweden: comparison with pharmaceutical sales. Ann Rheum Dis 2005;64:1805-7.
5. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
6. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.
7. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology Oxford 2003;42:244-57.
8. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796-806.
9. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
10. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 2005;52:2625-36.
11. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23 Suppl:S100-8.
12. Ekdahl C, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Use of a Swedish version of the Stanford Health Assessment Questionnaire. Scand J Rheumatol 1988;17:263-71.
13. Kristensen LE, Saxne T, Nilsson JA, Geborek P. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8:R174.
14. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 2005;64:1274-9.
15. Gulfe A, Geborek P, Saxne T. Response criteria for rheumatoid arthritis in clinical practice: how useful are they? Ann Rheum Dis 2005;64:1186-9.
16. Guidelines for Pharmacotherapy of Rheumatoid Arthritis. In: The Swedish Society for Rheumatology; 2004 [Swedish]. Internet. Accessed Dec 19, 2008. Available from: http://www.musconline.org/html/srf/images/documents/riktra04/riktrakort.pdf
17. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Probability of continued low disease activity in patients with recent onset rheumatoid arthritis treated according to the Disease Activity Score. Ann Rheum Dis 2008;67:266-9.
18. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226-35.
19. Smolen JS, Aletaha D, Grisar J, Redlich K, Steiner G, Wagner O. The need for prognosticators in rheumatoid arthritis. Biological and clinical markers: where are we now? Arthritis Res Ther 2008;10:208.