HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2015 September 03.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2011 June ; 63(6): 856–864. doi:10.1002/acr.20452.

Greater Likelihood of Remission in Rheumatoid Arthritis Patients Treated Earlier in Disease Course: Results from the CORRONA Registry

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Abstract

Objective—To examine whether disease duration is an independent predictor of achieving remission in rheumatoid arthritis (RA) patients initiating therapy.

Methods—RA patients in the CORRONA registry newly prescribed a nonbiologic disease modifying antirheumatic drug (nbDMARD) or anti-TNF with at least one follow-up visit were identified. Achievement of remission was defined using the Clinical Disease Activity Index (CDAI ≤ 2.8) and 28 joint Disease Activity Score (DAS28 < 2.6) at any follow-up visit within one year; sustained remission was defined as remission during any two successive visits. Likelihood of remission was examined through logistic regression based on 5 year increments of disease duration adjusting for baseline covariates.

Results—Among the 1,646 nbDMARD initiators, CDAI remission occurred in 21.3% of those with ≤ 5 years disease duration, 19.6% with 6–10 years and 13.5% with ≥ 11 years ($p<0.0001$); sustained remission occurred in 10.2%, 8.8% and 2.5% respectively ($p<0.001$). Results were similar among the 3,179 anti-TNF initiators (CDAI remission in 22.3%, 17.7%, and 12.8%

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DISCLOSURES

Dr. Furst serves as Director of Publications for CORRONA and has served on Advisory Boards for Abbott, Amgen, BMS, Centocor, Genentech, Bogen-Idec, Roche and UCB. Dr. Pangan is an employee of Abbott Laboratories. Dr. Harrold serves as a consultant to CORRONA and receives salary support from NIH (K23AR053856). Dr. Chang is a full-time employee of Tufts Medical Center and statistical consultant of CORRONA. Dr. Reed has a research contract through the University of Massachusetts with CORRONA. Dr. Kremer is President of CORRONA. He has served on Advisory Boards for BMS, Centocor, Roche and UCB and has received research support from Abbott, Amgen, BMS, Centocor, Genentech, Pfizer and Roche. Dr. Greenberg receives salary support from research grants from the NIH (K23AR054412), the Arthritis Foundation and Bristol Myers Squibb, serves as Chief Scientific Officer for CORRONA and has served on Advisory Boards for BMS, Centocor, Genentech, Roche and UCB.

respectively [(p<0.001]; CDAI sustained remission in 9.7%, 9.5% and 4.2% respectively [p<. 0.001]). DAS28 results were similar in both groups. In adjusted analyses, an increase of disease duration by 5 years was associated with a reduced likelihood of CDAI remission in nbDMARD (OR 0.91, 95% CI 0.83–0.99) and anti-TNF initiators (OR 0.88, 95% CI 0.83–0.94). A similar result was seen for sustained remission using CDAI (nbDMARD: OR 0.61, 95% CI 0.48–0.76; anti-TNF: OR 0.85, 95% CI 0.75 – 0.97).

Conclusions—Earlier treatment was associated with a greater likelihood of remission.

Keywords

rheumatoid arthritis; DMARD therapy; anti-TNF therapy; remission; disease duration

Remission, meaning the absence of disease activity, is the goal of therapy in rheumatoid arthritis. Earlier and more aggressive use of disease modifying anti-rheumatic agents (DMARDs) is being advocated with the goal of achieving remission.[1] For RA patients treated with non-biologic DMARDs (nbDMARDs) including methotrexate, there is some evidence that drug responsiveness may be influenced by disease duration.[2] Over the last decade, there has been increased attention to anti-tumor necrosis factor (anti-TNF) therapies and the potential impact they can have on remission. Anti-TNFs have demonstrated unprecedented efficacy for the treatment of rheumatoid arthritis (RA).[3–6] Clinical trials of anti-TNFs have been performed demonstrating efficacy for patients with both early and established RA.[5–7] However, because direct comparisons of response rates across trials with anti-TNFs in early versus established disease are not appropriate, it is unclear if the magnitude of response, or rates of achievement of remission are superior for patients with shorter duration of disease in a more typical clinical setting. We sought to examine the relationship between disease duration and achievement of remission and whether that was influenced by the class of treatment initiated. Specifically we sought to compare the rates of remission stratified by disease duration in those initiating nbDMARDs and anti-TNF agents.

Thus, the aim of the present study was to investigate the *a priori* hypothesis that RA disease duration was an independent predictor of achieving remission within one year of treatment regardless of DMARD class. We tested this hypothesis using a large U.S. cohort of RA patients with a broad range of disease duration from the Consortium of Rheumatology Researchers of North America (CORRONA) registry.

PATIENTS AND METHODS

Data source and population

The Consortium of Rheumatology Researchers of North America registry (CORRONA) is a prospective observational cohort of patients with arthritis who are enrolled by participating rheumatologists in both academic and private practice sites; the details have been previously published.[8, 9] There were 17,424 patients with rheumatoid arthritis and 91,832 visits in the CORRONA registry database from October 1, 2001 to November 1, 2008. No disease activity or comorbidity exclusion criteria were required for RA patients enrolled into the consortium registry. For the purposes of this study, this analysis was restricted to patients who initiated a nonbiologic DMARD or anti-TNF therapy, were not in remission at the

baseline visit and who had at least one visit within one year from baseline (we did not require continued use of a nbDMARD or an anti-TNF to be included in the analyses). Patients who initiated a different DMARD (biologic or nonbiologic) after having discontinued one prior to the baseline visit were included in the study (i.e., patients with prior DMARD exposure). We did not exclude patients who discontinued the initiated agent during the 1-year observation period or patients who switched agents. Approvals for data collection and analyses were obtained for academic and private practice sites from local and central institutional review boards, respectively.

Measures and Data Collection

Data are collected from both patients and their treating rheumatologists using standard clinical research forms, which gather information on disease severity and activity (including components of ACR and EULAR response criteria), medical comorbidities, use of medications including nonbiologic and biologic DMARDs, and adverse events. Among the data elements collected in the registry relevant to this study are a 28 tender and swollen joint count, physician and patient global assessments of disease activity, patient assessment of pain, the modified Health Assessment Questionnaire (mHAQ) assessing physical function, and erythrocyte sedimentation rate (ESR). Acute phase reactant data are recorded from laboratory tests obtained within 10 days of the clinical encounter, although collection of laboratory data is not mandated by the study protocol. Because the protocol does not mandate specific intervals between study visits, we included study visits within a 3-month time window of the one year study period. The scope of the data collected and comparison with other registries has been previously described.[10]

Primary and Secondary Outcomes

The baseline visit was defined as the visit when the agent (nonbiologic DMARD or anti-TNF therapy) was initiated or a visit prior to when the agent was begun if the initiation occurred between visits. Patients who were in “remission” at baseline based on the CDAI and DAS28 were identified and these patients were excluded from further analysis only when the analysis used the specific criteria for which they were defined to be in “remission” at baseline. We also limited the calculation of remission to patients with all the components necessary for the specific remission criteria of interest.

The primary outcome for remission was the CDAI ≤ 2.8 at any follow-up visit within one year of initiation. Because the ESR is not mandated at all study visits in the CORRONA registry, DAS28–defined remission (< 2.6 at any follow-up visit) was a secondary outcome. In addition, we evaluated for sustained remission defined as remission during any two consecutive visits, not including the first (baseline) visit, within one year after initiation. These results were stratified by disease duration (≤5 years, 6 to 10 years and ≥ 11 years).

Statistical Analyses

Patient clinical and demographic characteristics were compared among three disease duration groups. For continuous measures, means and standard deviations were estimated and the overall statistical differences among all three groups were tested using ANOVA, or

F test. For dichotomous measures, percentages were estimated and Fisher's exact test was used to test statistical differences among groups.

Unadjusted and adjusted odds ratios assessing the likelihood of remission as well as sustained remission after initiation based on disease duration (age was considered a continuous variable with patients grouped based on 5 year increments) were estimated using multivariable logistic regression models and were reported with estimated 95% confidence intervals. Covariates associated with remission were considered as possible confounders.[11] These covariates included patient demographics (age, gender, race, education and insurance status), calendar year of therapy initiation, RA disease duration, baseline disease activity, severity measures (mHAQ, disability, morning stiffness and fatigue), as well as current (concomitant prednisone and methotrexate) and prior medication usage (anti-TNFs and nonbiologic DMARDs). A backwards stepwise approach was used to identify potential variables to include in the model. In addition, variables thought from a clinical perspective to influence the likelihood of remission were forced into the model including age and gender. These models were run for both the CDAI and DAS28 remission outcomes. As sensitivity analyses, we examined the likelihood of remission and sustained remission in those who were nonbiologic DMARD naïve and biologic naïve at the time of initiation. We handled missing data using the most conservative approach without any value imputation. Patients with missing data for any of the variables in the final multivariate models were excluded from the models.

RESULTS

There were 1,646 patients who initiated a nonbiologic DMARD and 3,179 who initiated anti-TNF therapy as well as met inclusion criteria. The mean and median number of visits over the 1 year period was 2 for the groups. For analyzing sustained remission, we examined the 54–59% of patients with at least 3 visits. The vast majority of patients stayed on their medications during the 1 year period (84–87% of nonbiologic DMARD initiators and 79–82% of anti-TNF initiators). Remission based on the CDAI over the one year follow-up period occurred in 18.3% of nonbiologic DMARD initiators and 17.6% of anti-TNF initiators, while sustained remission occurred in 7.2% and 7.6% respectively in those with two or more follow-up visits. When we limited the population to those in which a DAS28 could be calculated, DAS28 remission occurred in 14.4 % and sustained remission in 3.5% of nonbiologic users (n=617). In anti-TNF initiators (n=1247), it was 20.0% and 7.9% respectively.

The baseline characteristics of RA patients with early and established disease included in the evaluation of remission are presented in Table 1. Those with earlier RA were more likely to be younger and working. Among anti-TNF initiators, those with earlier disease were more likely to be receiving concomitant methotrexate. Greater disease duration was associated with more exposure to disease modifying anti-rheumatic agents. Among the anti-TNF initiators, there were no significant differences in the specific agent prescribed. Disease levels at baseline were generally comparable, with the exception of those with 6 to 10 years of RA who were more likely to have low disease activity as compared to the other disease duration groups for both the nbDMARD and anti-TNF initiators. Similar results of baseline

characteristic comparisons were found when examining the biologic naïve anti-TNF initiators as well as when we compared RA patients who had 2 or more follow up visits, which was the sample used for the evaluation of sustained remission (data not shown).

The percentages of patients who achieved remission based on the CDAI over the follow-up period among the nbDMARD initiators was 21.3% in those with ≤ 5 years disease duration as compared to 19.6% in those with 6–10 years and 13.5% in those with ≥ 11 years (p=0.001) (Table 2). In the anti-TNF initiators the rates were 22.3%, 17.7% and 12.8% respectively (p<0.001). Similar results were found using the DAS28 in the anti-TNF initiators (24.1% vs. 21.2% vs. 15.0%, p=0.001). The DAS28 remission rates were somewhat lower among the 617 patients in the nbDMARD cohort who had the necessary data elements for the DAS28 calculation. The percentage of patients achieving sustained remission based on the CDAI was also greater for those with earlier disease duration among both the nbDMARD and anti-TNF initiators (nbDMARD initiators: 10.2% vs. 8.8% vs. 2.5%; p<0.001; anti-TNF initiators: 9.7% vs. 9.5% vs.4.2%; p<0.001). Similar estimates were obtained using the DAS28 among the anti-TNF initiators (8.9% vs. 11.6% vs.4.9% ; p=0.04)

Among the nbDMARD initiators, an increase of disease duration of 5 years was associated with a reduced likelihood of remission based on the CDAI (OR 0.91, 95% CI 0.83–0.99) in both unadjusted and adjusted analyses (Table 3). Greater disease duration was also associated with a reduced likelihood of achieving sustained remission based on the CDAI (OR 0.61, 95% CI 0.48–0.76) (Table 4). Using the DAS28 and a smaller study population, the estimates for remission and sustained remission were similar but the confidence intervals crossed unity.

Among the anti-TNF initiators, disease duration was associated with remission using both the CDAI (OR 0.88, 95% CI 0.83–0.94) and the DAS28 (OR 0.90, 95% CI 0.83 – 0.99) (Table 5). Greater disease duration was also associated with a reduced likelihood of achieving sustained remission based on the CDAI (OR 0.85, 95% CI 0.75–0.97). Using the DAS28, the estimate was similar but the confidence interval crossed unity (OR 0.89, 95% CI 0.75–1.06) (Table 6).

As a sensitivity analysis, we examined the relationship between disease duration and achievement of remission, as well as sustained remission, in those who were biologic naïve using logistic regression models (there were too few patients to examine rates in those initiating their first nbDMARD). There was a significant relationship between disease duration and likelihood of remission using the CDAI (OR 0.85, 95% CI 0.79–0.938 for a 5 year increase in RA disease duration), however the confidence interval crossed unity when using the DAS28 outcome definition (OR 0.97, 95% CI 0.86 – 1.09). This is likely related to the greater than 50% decrease in the sample size (1217 vs. 579) when the analyses were limited to those who were biologic naïve. Similar findings were demonstrated when examining the likelihood of sustained remission using the CDAI (OR 0.85, 95% CI 0.73 – 0.98) and DAS28 (OR 0.94, 95% CI 0.78 – 1.14).

DISCUSSION

In this large U.S. based cohort of RA patients, we report on remission rates achieved using nbDMARDs and anti-TNF agents based on RA disease duration through two well-recognized remission definitions. Interestingly, unadjusted CDAI remission and CDAI sustained remission rates were similar in the nonbiologic DMARD and anti-TNF initiators, particularly those with 5 ≤ years disease duration. In both unadjusted and adjusted analyses, initiation of nbDMARD and anti-TNFs in those with earlier disease was associated with a greater likelihood of remission and sustained remission using the CDAI. This was also seen using the DAS28 remission definition in anti-TNF initiators. Similar results were found when the analyses were limited to patients who were biologic naïve at the time of anti-TNF initiation.

Our results build upon the work of others who reported disease duration to be an important prognostic predictor of RA drug response. A meta-analysis of randomized controlled trials of non-biologic DMARDs including methotrexate demonstrated greater ACR response rates for patients with shorter disease duration.[2] However, remission outcomes were not examined and patients in the meta-analysis had markedly greater disease activity based on tender and swollen joints counts, ESRs and mHAQ scores than our U.S.-based cohort. In a *post-hoc* analysis of etanercept trials, patients with early RA had greater improvement in functional status as measured by the Health Assessment Questionnaire (HAQ) than those with established disease.[12] In a *post-hoc* analysis of the DE019 trial, which demonstrated the efficacy of adalimumab in patients with RA, there was a trend toward superior clinical, functional and radiographic outcomes in patients with early versus established disease.[13] These studies support our findings, in a large observational cohort, that disease duration is an important predictor of remission outcomes.

To our knowledge this is the first large clinical observational study showing greater remission rates associated with anti-TNF use stratified by disease duration. The largest published clinical study of remission and anti-TNF therapy was the Research in active RA trial (ReAct), an open-label trial of adalimumab.[14] The ReAct study population of 6,610 RA patients had remission rates of 27% by CDAI and 38% by DAS28.[14] The baseline level of disease activity in ReAct was greater than in the CORRONA cohort. Interestingly disease duration was not found to be a predictor of DAS28 remission. Similarly, in the British Society for Rheumatology Biologics Register (BSRBR), disease duration was neither a predictor of DAS28 remission nor response for patients prescribed etanercept (n=1267) or infliximab (n=1612), and they examined the influence of disease duration based on 10 year increments.[15] A third observational study from Italian investigators of 1,257 RA patients treated with anti-TNFs failed to identify disease duration as a predictor of remission, using 12 years as the cutpoint.[16]

Our findings differ from the results of the three European clinical studies and a number of differences may explain these discordant results. First, the study population of anti-TNF treated patients in the CORRONA U.S.-based registry included a large percentage of patients with less severe RA, with baseline joint counts and disease activity markedly lower than observed in the European studies. The many societal and health access reasons for this

disparity have been discussed in detail.[10] Briefly, the use of biologic drugs is much greater in the United States than in European societies because in Europe certain minimal disease characteristics are mandated in one-payer systems. Finally, the primary definition of remission is also different between studies. Since our results were similar using the CDAI and the DAS28 definitions, this gives us additional confidence in our findings

Interestingly, we found about 50% fewer patients in sustained remission compared with remission at one visit during the follow-up period. This suggests that many patients move in and out of remission, no matter how the remission is defined. It is likely that patients have ongoing disease activity even when they are characterized as being “in remission.” Nevertheless, we observed that disease duration was an independent predictor of sustained remission. To achieve and sustain remission in patients, treating rheumatologists will need to be diligent in detecting and documenting low levels of clinical disease activity. Sustained remission is probably preferable as it has been demonstrated that longer sustained remission, variously defined, was associated with less radiographic or functional deterioration and that shorter times in remission were associated with more radiographic progression.[17–20] However, X-ray progression may occur despite being in clinical remission.[21] Brown et al. demonstrated synovitis by ultrasound in some patients in clinical remission and this led to progression of radiographic joint damage.[22] Thus, all the clinical implications of patients who go in and out of remission, versus those who have a sustained remission, have not really been uniformly established. It is presently unclear if disability or quality of life issues are substantially different between these two therapeutic responses.

It is not surprising that prior anti-TNF use decreased the likelihood of achieving remission as the decision to discontinue is often based on response. Others have found that the effectiveness of anti-TNF agents were consistently superior for biologic-naïve versus biologic-experienced patients.[23–25] Similar findings were demonstrated in randomized controlled trials of new biologic agents, suggesting that patients with prior inadequate response to anti-TNF agents may represent a more treatment resistant population.[26] Interestingly, patients with greater functional impairment (indicated by a greater mHAQ score), disability and greater fatigue at baseline also have a decreased likelihood of achieving remission. Taken together with our observation of an enhanced clinical response in patients with earlier disease, it follows that patients with a high mHAQ score may have more advanced disease, and, thus, the anti-TNF agent was less likely to be effective. The same observation was noted in the nbDMARD initiators. However alternate hypotheses include the possibility that even earlier interventions will not be as effective in patients who already have established functional decline as they may have more treatment resistant disease and have an irreversible component to their functional disability that would be unresponsive even to effective therapies for RA. It is also possible that the components of the mHAQ can be related to alternative disease states, including secondary osteoarthritis, which would not necessarily be expected to respond to more aggressive interventions for RA.

Our study has certain limitations. Currently, there are several approaches to assess clinical remission. We used the CDAI as our primary remission measure, principally because this allowed for the inclusion of the greatest number of patients with complete measures. The

CDAI reflected the impact of disease duration on both remission and sustained remission in both the unadjusted and adjusted models, while the DAS28 showed effects only for remission (not sustained remission). This difference may have simply been the result of having fewer patients in the DAS28 group for which sustained remission could be assessed (CDAI group N= 1830 versus DAS28 group N=602 among the anti-TNF initiators). Also the CDAI is independent of the ESR, leaving it more freely responsive to the purely clinical measures. It is reassuring that the CDAI remission criteria are more stringent than the DAS28, in that these require less residual disease activity.[27] Our registry does not mandate radiographic imaging at predefined time periods, thus, our analyses could only focus on the attainment of clinical remission with nbDMARDs and anti-TNF therapies without examination of radiographic progression. Lastly, the patients with longer disease duration were more likely to be switching nonbiologic DMARD therapy rather than be first-time DMARD users and there were insufficient numbers of patients starting their first nonbiologic DMARD in order to analyze their results separately. Thus, it is difficult to disentangle the effect of disease duration from treatment resistant disease suggested by nonbiologic DMARD switching.

The strengths of our study include a very large number of “real-world” patients from a large U.S.-based registry, which includes detailed clinical data measurements derived from rheumatologists at the time of a clinical encounter. Many of the reports from registry data are derived from Europe where the overall disease activity tends to be substantially greater than that found within the U.S.[10] Thus, U.S. registry data are important for comparisons of clinical outcomes across different societal and political contexts.

In conclusion, the results of this U.S.-based study demonstrate that for every increase of disease duration of 5 years, the likelihood of remission and sustained remission are reduced by 10 to 15% in the adjusted models. Given that it represents a state with the least likelihood of disease progression, remission should be the therapeutic goal for patients and providers. To achieve this goal, our data lends further evidence that early and aggressive treatment of RA is an appropriate strategy in order to achieve remission as soon as possible after the onset of the disease. Patients and providers should strive for tight control, through serial assessment of disease activity, and by basing treatment decisions on these findings.

Acknowledgments

Funding: In the last two years, Abbott, Amgen, BMS, Centocor, Genentech, Lilly and Roche have supported CORRONA through contracted subscriptions to the database. Abbott, as part of its subscription contract, proposed the research study and was involved in the early design, as well as manuscript review and comment for this study. The final analysis plan, the study results and interpretations of the study data were those of the non-Abbott authors.

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Table 1

Baseline characteristics of patients included in the evaluation of remission stratified by disease duration.*

	RA disease duration							
	≤ 5 years N=784	6–10 years N=285	≥11 years N=577	P-value	≤ 5 years N=1295	6–10 years N=615	≥11 years N=1269	P-value
Demographics								
Male (% and N)	25.2 (197)	25.3 (72)	25.0 (144)	0.994	21.9 (283)	22.6 (139)	20.2 (256)	0.407
Age (Mean and SD)	56.9 (13.4)	59.3 (12.6)	64.4 (11.5)	<0.001	54.3 (13.6)	54.1 (12.6)	60.5 (11.5)	<0.001
Race				0.530				0.973
White (% and N)	81.0 (631)	84.0 (236)	85.1 (485)		84.6 (1084)	84.7 (515)	84.2 (1053)	
Black (% and N)	6.9 (54)	5.3 (15)	5.8 (33)		4.8 (62)	4.6 (28)	4.9 (61)	
Hispanic (% and N)	9.8 (76)	7.8 (22)	6.5 (37)		7.9 (101)	7.6 (46)	7.5 (94)	
Asian (% and N)	0.9 (7)	1.1 (3)	0.7 (4)		1.2 (15)	1.3 (8)	1.2 (15)	
Education				0.025				0.429
Some high school	8.2 (61)	6.7 (18)	9.2 (50)		6.3 (76)	7.0 (40)	6.2 (73)	
High school diploma	41.7 (312)	47.6 (127)	49.4 (268)		41.0 (498)	38.8 (223)	43.4 (512)	
College	50.1 (375)	45.7 (122)	41.3 (224)		52.8 (641)	54.3 (312)	50.4 (594)	
Working status (% and N)				<0.001				<0.001
Full time	42.8 (331)	37.9 (106)	18.6 (105)		45.3 (581)	42.4 (258)	23.8 (300)	
Part time	11.4 (88)	8.6 (24)	8.3 (47)		10.8 (139)	9.9 (60)	9.1 (114)	
Not working	14.4 (111)	12.9 (36)	14.3 (81)		12.5 (160)	12.5 (76)	16.1 (202)	
Retired	24.8 (192)	25.0 (70)	38.5 (218)		20.3 (260)	17.8 (108)	28.5 (359)	
Disabled	6.2 (48)	15.7 (44)	20.1 (114)		9.8 (126)	16.8 (102)	22.3 (281)	
Insurance								
Private (% and N)	73.2 (449)	74.7 (171)	64.1 (278)	0.002	81.7 (859)	78.6 (386)	70.5 (725)	<0.001
Medicare (% and N)	29.5 (181)	36.2 (83)	62.2 (270)	<0.001	23.6 (248)	25.5 (125)	46.4 (477)	<0.001
Medicaid (% and N)	8.0 (49)	7.0 (16)	11.5 (50)	0.072	5.0 (53)	7.9 (39)	10.3 (106)	<0.001
Clinical								
Morning stiffness in hours (Mean and SD)	1.4 (2.6)	1.3 (2.1)	1.6 (3.2)	0.249	1.6 (2.9)	1.5 (2.9)	1.5 (2.6)	0.290
Disease duration in years (Mean and SD)	2.1 (1.6)	7.8 (1.4)	20.5 (9.0)	<0.001	2.5 (1.6)	7.7 (1.5)	20.3 (8.4)	<0.001

	RA disease duration							
	≤ 5 years N=784	6–10 years N=285	≥11 years N=577	P-value	≤ 5 years N=1295	6–10 years N=615	≥11 years N=1269	P-value
Swollen Joints 28 (Mean and SD)	6.5 (6.4)	5.5 (5.6)	6.2 (6.0)	0.051	7.4 (6.7)	6.9 (6.5)	7.1 (6.3)	0.254
Tender Joints 28 (Mean and SD)	5.8 (6.1)	5.0 (6.0)	4.8 (5.7)	0.008	6.8 (7.0)	6.4 (6.8)	6.6 (6.6)	0.534
Patient Global	36.5 (25.4)	38.0 (25.6)	41.0 (25.3)	0.004	41.4 (25.6)	42.2 (25.6)	44.1 (26.2)	0.022
Assessment (Mean and SD)								
Patient VAS Pain (Mean and SD)	39.6 (26.6)	39.4 (25.5)	42.0 (25.7)	0.207	44.1 (25.9)	44.2 (25.8)	45.4 (26.4)	0.396
mHAQ (Mean and SD)	0.4 (0.5)	0.4 (0.5)	0.5 (0.5)	0.006	0.5 (0.5)	0.5 (0.5)	0.6 (0.5)	<0.001
ESR (Mean and SD)	25.6 (21.1)	23.0 (18.7)	28.2 (22.0)	0.069	24.3 (20.8)	26.4 (22.8)	29.0 (22.9)	0.002
DAS28 (Mean and SD)	4.3 (1.4)	4.2 (1.5)	4.3 (1.4)	0.670	4.4 (1.4)	4.5 (1.5)	4.6 (1.5)	0.093
CDAI (Mean and SD)	18.9 (12.9)	17.1 (12.2)	18.3 (12.3)	0.108	21.8 (13.7)	21.0 (13.8)	21.5 (13.1)	0.504
Disease Activity								
High (CDAI ≥22) (% and N)	47.7 (374)	41.1 (117)	43.8 (253)	0.112	57.5 (744)	53.0 (326)	57.5 (730)	0.132
Moderate (CDAI 10–22) (% and N)	30.0 (235)	30.2 (86)	34.7 (200)	0.156	28.0 (363)	28.8 (177)	29.2 (371)	0.794
Low (CDAI 2.8–10) (% and N)	22.3 (175)	28.8 (82)	21.5 (124)	0.044	14.5 (188)	18.2 (112)	13.2 (168)	0.016
Depression in last 8 weeks (% and N)	19.6 (154)	14.7 (42)	18.4 (106)	0.187	20.0 (259)	21.1 (130)	19.1 (242)	0.564
Fatigue in last 8 weeks (% and N)	29.3 (230)	25.3 (72)	27.0 (156)	0.368	33.4 (433)	30.6 (188)	30.3 (384)	0.185
Medication Use								
Concomitant prednisone (% and N)	34.6 (270)	31.6 (89)	40.2 (231)	0.025	42.5 (544)	36.7 (224)	44.0 (555)	0.010
Concomitant methotrexate (% and N)	N/A	N/A	N/A	N/A	72.3 (936)	62.8 (386)	67.7 (859)	<0.001
Prior DMARD use** (% and N)	80.5 (631)	95.1 (271)	93.8 (541)	<0.001	41.5 (538)	60.8 (374)	63.7 (808)	<0.001
Number prior DMARDs (Mean and SD)	1.2 (0.9)	1.8 (1.0)	2.0 (1.2)	0.0000	2.1 (1.4)	3.0 (1.6)	3.4 (1.9)	<0.001

*Abbreviations: CDAI= clinical disease activity index; DAS28= 28 joint disease activity score; DMARD= disease modifying anti-rheumatic drug; ESR= erythrocyte sedimentation rate; mHAQ= modified health assessment questionnaire; RA=rheumatoid arthritis; TNF=tumor necrosis factor; VAS=visual analogue scale

**prior DMARD use represented prior nonbiologic DMARD use for the nonbiologic DMARD initiators and prior anti-TNF use for the anti-TNF initiators

Table 2

Percentages of patients going into remission within one year as well as those with sustained remission grouped according to initiated drug class (nonbiologic DMARD versus anti-TNF), disease duration and remission definition.*

	RA disease duration			
	≤ 5 years	6–10 years	≥ 11 years	P value
Nonbiologic DMARD initiators				
Remission				
CDAI (n=1646)	21.3	19.6	13.5	<0.001
DAS28 (n=617)	16.9	15.0	10.7	0.138
Sustained remission				
CDAI (N=892)	10.2	8.8	2.5	<0.001
DAS28 (N=316)	2.1	7.4	3.4	0.192
Anti-TNF initiators				
Remission				
CDAI (n=3170)	22.3	17.7	12.8	<0.001
DAS28 (n=1247)	24.1	21.2	15.0	0.001
Sustained remission				
CDAI (n=1864)	9.7	9.5	4.2	<0.001
DAS28 (n=730)	8.9	11.6	4.9	0.04

* Abbreviations: CDAI= clinical disease activity index; DAS28= 28 joint disease activity score; DMARD= disease modifying anti-rheumatic drug; RA=rheumatoid arthritis

Table 3

The adjusted likelihoods of achieving remission based on the CDAI and DAS28 in nonbiologic DMARD users.*

	CDAI N=1538	DAS28 N=582
RA disease duration**	0.91 (0.83, 0.99)	0.94 (0.81, 1.10)
Other Covariates***		
Age	0.92 (0.83, 1.03)	0.94 (0.78, 1.14)
Female gender	0.64 (0.48, 0.86)	0.52 (0.30, 0.90)
High school education	0.61 (0.38, 0.97)	1.21 (0.41, 3.60)
College education	0.77 (0.48, 1.23)	2.04 (0.68, 6.06)
Disabled	0.33 (0.16, 0.67)	0.48 (0.16, 1.42)
mHAQ	0.50 (0.34, 0.75)	0.53 (0.26, 1.11)
Fatigue	0.97 (0.70, 1.36)	0.80 (0.44, 1.47)
Prednisone	0.65 (0.48, 0.88)	0.40 (0.22, 0.72)
MTX	1.04 (0.78, 1.39)	1.13 (0.64, 2.00)
Concomitant DMARD	1.12 (0.83, 1.52)	1.87 (1.05, 3.34)
Prior DMARD use	0.74 (0.47, 1.15)	0.49 (0.23, 1.05)
Baseline disease activity	0.97 (0.96, 0.99)	0.63 (0.47, 0.83)

* Abbreviations: CDAI= clinical disease activity; DAS28= 28 joint disease activity scale; DMARD= disease modifying anti-rheumatic drugs; mHAQ= modified health assessment questionnaire; MTX=methotrexate; RA=rheumatoid arthritis. Results are presented as Odds Ratios with 95% confidence intervals in parentheses.

** Odds ratio for every increase of 5 years in disease duration

*** Odds ratio of age is for an increase of 10 years. The odds ratios for the mHAQ and baseline disease activity are for one unit change of the underlying variables. For the remaining variables the odds ratios relate to the presence (as opposed to absence) of the variable.

Table 4

The adjusted likelihoods of achieving sustained remission based on the CDAI and DAS28 among nonbiologic DMARD initiators.*

	CDAI N=868	DAS28 N=309
RA Disease Duration**	0.61 (0.48, 0.76)	0.89 (0.63, 1.27)
Other Covariates***		
Age	0.87 (0.70, 1.08)	1.16 (0.61, 2.24)
Female gender	1.00 (0.53, 1.92)	0.10 (0.02, 0.52)
Disabled	0.38 (0.09, 1.63)	0.88 (0.12, 6.25)
mHAQ	0.43 (0.18, 1.04)	0.11 (0.01, 1.27)
Fatigue	0.32 (0.13, 0.76)	1.15 (0.22, 6.05)
Prednisone	0.42 (0.21, 0.83)	0.16 (0.02, 1.30)
MTX	2.04 (1.12, 3.71)	2.87 (0.57, 14.55)
Concomitant DMARD	0.97 (0.53, 1.79)	3.39 (0.71, 16.15)
Prior DMARD use	1.22 (0.45, 3.34)	1.07 (0.13, 8.86)
Baseline disease activity	0.99 (0.96, 1.02)	1.61 (0.87, 3.00)

* Abbreviations: CDAI= clinical disease activity; DAS28= 28 joint disease activity scale; DMARD= disease modifying anti-rheumatic drugs; mHAQ= modified health assessment questionnaire; MTX=methotrexate; RA=rheumatoid arthritis. Results are presented as Odds Ratios with 95% confidence intervals in parentheses.

** Odds ratio for every increase of 5 years in disease duration

*** Odds ratio of age is for an increase of 10 years. The odds ratios for the mHAQ and baseline disease activity are for one unit change of the underlying variables. For the remaining variables the odds ratios relate to the presence (as opposed to absence) of the variable.

Table 5

The adjusted likelihoods of achieving remission based on the CDAI and DAS28 among anti-TNF initiators.*

	CDAI N=3106	DAS28 N=1217
RA disease duration**	0.88 (0.83–0.94)	0.90 (0.83–0.99)
Other Covariates***		
Age	0.95 (0.88–1.03)	0.89 (0.80–1.00)
Female gender	0.92 (0.73–1.16)	0.67 (0.47–0.94)
Disabled	0.49 (0.33–0.74)	0.56 (0.31–0.99)
mHAQ	0.45 (0.34–0.59)	0.93 (0.63–1.36)
Fatigue	0.72 (0.57–0.91)	0.68 (0.48–0.96)
Concomitant prednisone	0.74 (0.60–0.90)	0.99 (0.73–1.33)
Concomitant MTX	1.36 (1.08–1.70)	1.46 (1.02–2.09)
Baseline disease activity	0.56 (0.46–0.69)	0.58 (0.43–0.79)
Prior anti-TNF use	0.98 (0.97–0.99)	0.62 (0.54–0.72)

* Abbreviations: CDAI= clinical disease activity index; DAS28= 28 joint disease activity scale; mHAQ= modified health assessment questionnaire; MTX= methotrexate; RA=rheumatoid arthritis; TNF=tumor necrosis factor. Results are presented as Odds Ratios with 95% confidence intervals in parentheses.

** Odds ratio for every increase of 5 years in disease duration

*** Odds ratio of age is for an increase of 10 years. The odds ratios for the mHAQ and baseline disease activity are for one unit change of the underlying variables. For the remaining variables the odds ratios relate to the presence (as opposed to absence) of the variable.

Table 6

The adjusted likelihoods of achieving sustained remission based on the CDAI and DAS28 among anti-TNF initiators.*

	CDAI N=1830	DAS28 N=602
RA Disease Duration**	0.85 (0.75–0.97)	0.89 (0.75, 1.06)
Other Covariates***		
Age	0.91 (0.79–1.04)	0.79 (0.63–1.00)
Female gender	0.99 (0.65–1.53)	0.43 (0.23–0.82)
Disabled*****	0.25 (0.08–0.79)	--
mHAQ	0.35 (0.19–0.62)	0.53 (0.24–1.16)
Fatigue	0.67 (0.43–1.04)	0.46 (0.21–1.03)
Concomitant prednisone	0.69 (0.47–1.00)	0.74 (0.40–1.37)
Concomitant MTX	1.55 (1.00–2.42)	2.83 (1.18–6.80)
Baseline disease activity	0.57 (0.39–0.84)	0.37 (0.19–0.73)
Prior anti-TNF use	0.98 (0.96–1.00)	0.72 (0.54–0.94)

* Abbreviations: CDAI= clinical disease activity; DAS28= 28 joint disease activity scale; mHAQ= modified health assessment questionnaire; MTX=methotrexate; RA=rheumatoid arthritis; TNF=tumor necrosis factor. Results are presented as Odds Ratios with 95% confidence intervals in parentheses.

** Odds ratio for every increase of 5 years in disease duration

*** Odds ratio of age is for an increase of 10 years. The odds ratios for the mHAQ and baseline disease activity are for one unit change of the underlying variables. For the remaining variables the odds ratios relate to the presence (as opposed to absence) of the variable.

**** There were too few patients to examine whether disability influenced the likelihood of sustained remission using the DAS28