Functional Improvement After Patients with Rheumatoid Arthritis Start a New Disease Modifying Antirheumatic Drug (DMARD) Associated with Frequent Changes in DMARD: The CORRONA Database

VEENA K. RANGANATH, HAROLD E. PAULUS, ALINA ONOFREI, DINESH KHANNA, GEORGE REED, DAVID A. ELASHOFF, JOEL M. KREMER, and DANIEL E. FURST

ABSTRACT. ***Objective.*** We examined the relationships of rheumatoid arthritis (RA), disease duration (DD), number of previous disease modifying antirheumatic drugs (DMARD), and frequency of DMARD changes, with regard to changes in function in patients with RA evaluated by modified Health Assessment Questionnaire (mHAQ) after the start of a new DMARD.

Methods. In total, 889 patients with active RA from the CORRONA database [patients had mHAQ ≥ 0.5 and/or Disease Activity Score 28-joint count (DAS28) ≥ 1.6] started a new DMARD (baseline) and had at least one followup visit 6–12 mo later. Change in mHAQ from baseline to followup visit was modeled using univariate/multivariate linear regression analysis. Due to colinearity, separate multivariate regression models were performed including/excluding the predictors disease duration, number of prior DMARD, and frequency of DMARD changes.

Results. Baseline age, mHAQ, erythrocyte sedimentation rate (ESR), DAS28, and number of prior DMARD differed across DD groups. The univariate linear regression model showed that higher baseline values of mHAQ, DAS28, swollen joint count (SJC), tender joint count (TJC), Clinical Disease Activity Index (CDAI), ESR, physician global assessment, prednisone use, and subsequent addition/discontinuation of DMARD were associated with improvement of the mHAQ at followup ($p = 0.05$). Multivariate linear regression models showed that mHAQ improvement was associated with shorter DD, higher baseline mHAQ, addition of subsequent DMARD, and the DMARD frequency index (no. previous DMARD/yrs of DD) ($p < 0.05$). Number of DMARD patients used previously was not associated with change of mHAQ in either model.

Conclusion. Our study demonstrates that in clinical rheumatologic practices, more frequent changes in DMARD are associated with greater improvement in function (by mHAQ). It does not support the idea that number of previous DMARD used predicts response. Indirectly, these data support the concept that DMARD should be changed if optimal responses are not achieved within a specified time.

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Rheumatoid arthritis (RA) is an inflammatory destructive arthritis of unclear etiology that affects roughly 1% of the general population. Although there is no cure for RA, disease modifying antirheumatic drugs (DMARD) are the mainstay of therapy and are used to decrease the rate of joint destruction, reduce inflammation, and improve quality of life.

With the expanding repertoire of DMARD available for the treatment of RA, it may be important to evaluate the influence of the DMARD previously used on response to a

From the Department of Medicine, Division of Rheumatology, University of California, Los Angeles, California; University of Massachusetts Medical School, Worcester, Massachusetts; and Center for Rheumatology, Albany Medical College, Albany, New York, USA.

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V.K. Ranganath, MD; H.E. Paulus, Department of Medicine, Division of Rheumatology, University of California, Los Angeles; A. Onofrei, University of Massachusetts Medical School; D. Khanna, MD, Department of Medicine, Division of Rheumatology, University of California, Los Angeles; G. Reed, PhD, University of Massachusetts Medical School; D.A. Elashoff, PhD, Department of Medicine, University of California, Los Angeles; J.M. Kremer, MD, Center for Rheumatology, Albany Medical College; D.E. Furst, MD, Department of Medicine, Division of Rheumatology, University of California, Los Angeles.

Address reprint request to Dr. V.K. Ranganath, Department of Medicine, Division of Rheumatology, UCLA, Rehabilitation Center, Room 32-59, 1000 Veteran Avenue, Los Angeles, CA 90095-1670.
E-mail: vranganath@mednet.ucla.ed

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new DMARD. Since the ultimate goal of RA treatment is to attain and sustain remission, rheumatologists are being encouraged to change DMARD if the current therapy does not achieve preset goals for benefit within a predetermined time, in order to reduce a patient's disease activity[1,2]. The effect of a treatment strategy of tight control for RA (the TICORA study) assessed an aggressive RA outpatient management strategy with a goal of Disease Activity Score (DAS) < 2.4, and the BeSt study evaluated 4 common but different RA treatment strategies. The results of these 2 studies demonstrated that aggressive management of RA is the optimal therapeutic approach, and stressed the importance of changing a patient's treatment regimen if the response is not achieved.

Thus, the frequency or rate of DMARD changed might be used to identify patients with aggressive DMARD management, which may result in less disease activity and better function[1,2]. We hypothesized that the "DMARD frequency index" (the ratio of the number of previous DMARD used per disease duration in years) is associated with a better outcome.

There have been many efforts to identify important demographic and disease activity factors influencing physical function responses to the use of DMARD. Metaanalyses of published reports of clinical trials suggest that patients with longer RA disease duration respond to DMARD less well than those with shorter disease duration when evaluated with physical function measures[3-9]. In addition, several reports evaluated the use of previous DMARD as a predictor of efficacy when a new DMARD was started[4,8,10-12]. Some reports have suggested that inadequate response to previous DMARD was associated with decreased response to the next DMARD[4,8,10-12].

We examined potential factors associated with improvement measured by modified Health Assessment Questionnaire (mHAQ) in a large cohort of community-based patients with RA, with specific emphasis on disease duration, number of prior DMARD used, and the rate of DMARD changes.

MATERIALS AND METHODS

Patients. The CORRONA database was assembled for the purpose of facilitating cohort studies in rheumatologic diseases by accumulating longitudinal "real-world" data representing community patients with rheumatic disease. This registry was started in the spring of 2002 and continues to recruit and follow patients.

As of July 2006, 11,255 patients with RA from 76 different sites and > 200 rheumatologists in the United States had been enrolled in the CORRONA registry. At entry, patients complete a patient enrollment questionnaire, including the mHAQ (see details below)[13]. The patient enrollment questionnaire includes information regarding medical history, surgical history, family history, review of symptoms, and medication use. The patient entry and followup questionnaires include detailed information on DMARD therapy and corticosteroids. At subsequent patient visits, followup questionnaires review symptoms over the last 8 weeks and current medication use. The physician review form includes a list of current rheumatic diagnoses, recent hospitalizations, current clinical information, infections, comorbidities, radiological reports, and laboratory findings (hematocrit, platelet count, etc). Clinical information includes 28 tender joint count (TJC), 28 swollen joint count (SJC), physician global assessment (0–100 visual analog scale), rheumatoid factor (RF) positivity, extraarticular manifestations, and acute-phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as available]. The patient completes the mHAQ in the office.

Methods. The mHAQ presents the patient with one question from each of the 8 domains of the HAQ Damage Index (HAQ-DI; dressing, rising, eating, walking, hygiene, reach, grip, and usual activities). Each item is scored from 0 to 3, 0 meaning that the patient is able to do the activity with no difficulty, and 3 that the patient is unable to do the task. The items are averaged so that the final mHAQ score is between 0 and 3. Because there are no validated, dichotomous cutpoints to define patient clinical improvement or minimal clinically important differences for the mHAQ[14], we used the mHAQ as a continuous variable for our outcome measure to evaluate improvement. The change in mHAQ was calculated by subtracting baseline mHAQ from the followup mHAQ at the last visit within the 6–12 month interval.

For our analysis, the cohort was limited by predefined criteria to those RA patients who started a new DMARD and for whom the mHAQ was ≥ 0.5 or DAS was ≥ 1.6 at baseline. Clinical remission is considered the main therapeutic target in RA. However, recent studies have shown that radiographic progression continues despite the satisfaction of remission criteria. Thus, the strictest definition of remission by DAS was used (i.e., DAS ≤ 1.6). Baseline was considered the start of the new DMARD. Patients also were required to have at least one followup assessment within 6–12 months (889 patients). We also performed a similar analysis with a control cohort (data not shown). The control cohort consisted of RA patients who were stable under treatment with DMARD/biologics/steroids (same dose) and had an interval of time between 6 and 12 months remaining on stable therapy. If a patient had more than one visit still on stable therapy and within 6 and 12 months, then we used the last visit in that time interval for analysis. The stable cohort was not analyzed in combination with the DMARD-change cohort. In the analyses of the stable cohort we included the covariates of age, sex, and disease activity in the models for mHAQ change.

The following clinical and laboratory factors were considered as potential predictors of treatment response, all at baseline: disease duration, age, sex, prednisone use, mHAQ, physician global assessment, swollen joint count, tender joint count, ESR, Clinical Disease Activity Index (CDAI), DAS 28-joint count (DAS28), RF positivity, number of prior DMARD, number of DMARD ever used, DMARD added after baseline, DMARD discontinued after baseline, ethnicity, and education level. Patients were further subcategorized by physician-documented disease duration into < 3 years, 3–5 years, and > 5 years (Table 1). In addition, we developed a DMARD frequency index, which is number of DMARD used previously divided by patient's disease duration (yrs).

Statistical analysis. We compared baseline characteristics of RA patients among the 3 disease-duration groups (< 3 yrs, 3–5 yrs, > 5 yrs) using one-way analysis of variance (ANOVA). ANOVA was also used to compare the change scores of study measures (baseline minus followup) among the disease-duration groups. Univariate and multiple linear regression models were used to evaluate predictors of change of mHAQ in response to starting a new DMARD. Stepwise model selection was used to select variables for the multiple linear regression models. Disease duration and number of DMARD ever used were forced into these models even if not included by the model selection criterion. As an additional model, we included the DMARD frequency index rather than disease duration and number of DMARD ever used. All 3 variables were not used in the same model, as the DMARD frequency index is a direct function of disease duration and number of previous DMARD.

RESULTS

A total of 889 patients with RA who started taking a new

Table 1. Patients' baseline characteristics and change from baseline to followup 6–12 months later.

	Duration of RA			
	< 3 yrs	3–5 yrs	> 5 yrs	p
Baseline Characteristics				
No. of patients	150	155	584	
Age, yrs (SD)	56 (14.6)	56 (13.7)	60 (12.0)	< 0.001
White, %	82	84	84	NS
College education, %	44	48	43	NS
Female, %	77	75	77	NS
RF+ ever, %	75	76	77	NS
Prednisone dose, mg/day (SD); no. of patients using	5.6 (2.9); n = 64	6.0 (2.9); n = 54	5.6 (2.9); n = 247	NS
mHAQ (0–3), (SD)	0.57 (0.5)	0.47 (0.4)	0.61 (0.5)	0.005
SJC28 (SD)	6.0 (6.3)	6.8 (6.3)	6.5 (6.0)	NS
TJC28 (SD)	5.8 (6.9)	5.8 (6.4)	5.8 (6.2)	NS
ESR, mm/h (SD)	23 (18.4)	25 (19.7)	28 (22.8)	0.037
DAS28 (SD)	3.9 (1.5)	4.0 (1.3)	4.3 (1.4)	0.017
CDAI (0–76), (SD)	18 (13.9)	18 (12.6)	20 (12.9)	NS
No. of DMARD ever (SD)	1.08 (0.9)	1.9 (1.5)	2.55 (1.9)	< 0.001
DMARD frequency index* (SD)	0.80 (0.7)	0.51 (0.4)	0.19 (0.2)	< 0.001
Change from baseline to followup 6–12 months later				
Months from initiation of new DMARD, at baseline (SD)	9.2 (1.8)	9.3 (1.7)	9.3 (1.7)	NS
No. of patients	150	155	584	
Change in prednisone dose, mg/day (SD)	–0.7 (2.6)	–0.3 (2.7)	0.01 (2.8)	0.016
Discontinued prednisone, %	15	5	6	0.001
mHAQ (0–3), (SD)	–0.13 (0.5)	–0.03 (0.4)	–0.07 (0.4)	NS
SJC28 (SD)	–1.4 (6.6)	–1.8 (5.8)	–1.6 (5.7)	NS
TJC28 (SD)	–1.6 (7.8)	–1.0 (6.6)	–1.4 (6.8)	NS
ESR, mm/h (SD)	–1.6 (12.3)	–1.1 (16.8)	–2.3 (16.4)	NS
DAS28 (SD)	–0.29 (1.4)	–0.39 (1.4)	–0.46 (1.4)	NS
CDAI (0–76), (SD)	–4.3 (16.4)	–3.4 (13.6)	–4.6 (13.7)	NS
DMARD added, % of patients	8.0	5.2	5.8	NS
DMARD discontinued, % of patients	10.7	14.2	9.8	NS

* Number of DMARD ever used divided by disease duration in years. For 877 observations (12 missing because duration was "0"); mean = 0.35 (SD 0.42), median = 0.2, range 0–3.33. RF: rheumatoid factor; mHAQ: modified Health Assessment Questionnaire; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score 28-joint count; CDAI: Clinical Disease Activity Index; DMARD: disease modifying antirheumatic drug; NS: nonsignificant.

DMARD and who had at least one followup assessment within 6–12 months were included in the cohort. Baseline characteristics for patients with disease duration < 3 years, 3–5 years, and > 5 years are described in Table 1. There was no difference among the 3 groups in ethnicity, education, and RF positivity. However, baseline mHAQ scores, age, ESR, DAS28, and number of previous DMARD differed across the disease-duration categories (p = 0.005, < 0.001, 0.037, 0.017, and < 0.001, respectively). Change from baseline to followup time was evaluated across disease-duration categories (Table 1). Decrease of prednisone dose and discontinuation of prednisone were more likely in those with < 3 years' RA duration (p = 0.016).

The association of change in mHAQ with the number of DMARD previously used per year of disease duration was evaluated (Table 2). There was a significant association between the DMARD frequency index and the amount of improvement in the mHAQ, i.e., more frequent DMARD changes were associated with improvement in mHAQ (p = 0.02).

The results of the univariate linear regression model showed that RA patients with higher baseline mHAQ, prednisone use, DAS28, SJC, TJC, ESR, CDAI, and physician global assessment were associated with mHAQ improvement during 6–12 month followup (Table 2). The number of DMARD ever used and disease duration did not correlate with change in mHAQ with the univariate analysis. However, the addition or discontinuation of a DMARD after baseline did correlate with improvement of mHAQ (p = 0.012, p = 0.026, respectively).

The multivariate linear regression model for change in mHAQ as an outcome measure (without disease duration) demonstrated that baseline mHAQ score, DMARD frequency index, and addition of a new DMARD during followup were predictors of mHAQ response (overall model $r^2 = 0.19$; Table 3). The multivariate regression model using disease

Table 2. Univariate linear regression analysis, change in mHAQ during 6–12 months followup.

	Estimate (Δ in mHAQ)	CI	p
Duration (per 10yrs)	0.01	(–0.01, 0.04)	NS
Duration groups			
< 3 yrs	Referent		
3–5 yrs	0.096	(–0.00, 0.19)	0.040
> 5 yrs	0.060	(–0.01, 0.13)	NS
DMARD Groups*			
A	Referent		
B	–0.030	(–0.09, 0.03)	NS
C	0.040	(–0.08, 0.16)	NS
No. of DMARD ever used			
0	Referent		
1	–0.02	(–0.11, 0.07)	NS
2	–0.02	(–0.11, 0.07)	NS
3	–0.06	(–0.16, 0.04)	NS
≥ 4	–0.07	(–0.17, 0.03)	NS
Age (per 10 yrs)	0.02	(0.00, 0.04)	0.084
Female	–0.03	(–0.09, 0.04)	NS
White	0.02	(–0.05, 0.09)	NS
College education	0.01	(–0.04, 0.07)	NS
Prednisone use	–0.06	(–0.12, –0.01)	0.028
DMARD frequency index†	–0.075	(–0.14, –0.01)	0.020
DMARD added	–0.14	(–0.26, 0.03)	0.012
DMARD discontinued	–0.10	(–0.19, –0.01)	0.026
Baseline variables			
mHAQ	–0.302	(–0.35, –0.25)	< 0.001
DAS28	–0.50	(–0.72, –0.28)	< 0.001
SJC	–0.07	(–0.11, –0.03)	0.002
TJC	–0.08	(–0.12, –0.04)	< 0.001
ESR	–0.02	(–0.04, –0.01)	0.001
CDAI	–0.06	(–0.08, –0.04)	< 0.001
Physician global	–0.03	(–0.04, –0.02)	< 0.001
RF+	–0.02	(–0.10, 0.05)	NS
No. of prior DMARD used	–0.01	(–0.03, 0.00)	NS

* (A) TNF inhibitors or if the patient was started on more than one DMARD at baseline; (B) methotrexate, leflunomide, sulfasalazine, immuran, or cyclosporine started; (C) hydroxychloroquine or minocycline started. † DMARD frequency index is the ratio of number of previous DMARD divided by disease duration in years. For definitions see Table 1.

Table 3. Multiple linear regression, change in mHAQ versus baseline values (including the frequency of DMARD changes variable).

Covariates	6–12 Months' Followup, n = 851		
	Estimate (Δ in mHAQ)	CI	p
DMARD frequency index*	–0.064	–0.123, –0.005	0.034
mHAQ	–0.299	–0.35, –0.25	< 0.001
DMARD added	–0.196	–0.30, –0.09	< 0.001

* Ratio of number of previous DMARD divided by disease duration (years). DMARD: disease modifying antirheumatic drug; mHAQ: modified Health Assessment Questionnaire.

Table 4. Multiple linear regression, change in mHAQ versus baseline values.

Covariates	6–12 Months' Followup, n = 863		
	Estimate (Δ in mHAQ)	CI	p
Disease duration (per 10 yrs)	0.027	0.002, 0.052	0.036
No. prior DMARD	–0.001	–0.016, 0.013	NS
mHAQ	–0.315	–0.37, –0.26	< 0.001
DMARD added	–0.131	–0.30, –0.09	< 0.001

DMARD: disease modifying antirheumatic drug; mHAQ: modified Health Assessment Questionnaire; NS: nonsignificant.

duration showed similar results (Table 4). The number of DMARD ever used was not associated with change in mHAQ in any analysis.

A similar analysis was performed using a cohort of 1594 CORRONA patients with RA who were stable taking DMARD/biologics/steroids (same dose) and had an interval of time between 6 and 12 months remaining on stable therapy (data not shown). The results showed that the stable-

therapy cohort had a mean disease duration of 12.2 versus 11.9 years in the cohort starting a new DMARD. As expected, in this stable-DMARD cohort mHAQ increased over time (i.e., worsened; mean change +0.02, 95% CI 0.007, 0.033, p = 0.002). In contrast, the mean change in mHAQ after initiation of a DMARD in the study cohort was –0.07 (a significant, although small, improvement).

DISCUSSION

Our study evaluated a large cohort of patients with RA who started a new DMARD while being followed by a large, representative sample of rheumatologists. The patients were evaluated for factors associated with functional improvement (measured by the mHAQ), using the prospective CORRONA database. This database is unique because of its overall size and its representation of data from > 200 community rheumatologists throughout the United States. It represents a geographically diverse (Northeast, Southeast, Midwest, Northwest, and Southwest of the USA) and generally representative sample of US clinical rheumatology practice. Our original hypothesis posited that RA patients with longer disease duration and those who had used more previous DMARD might be less responsive to the next DMARD and thus would not improve their mHAQ (i.e., function) as much as those exposed to fewer DMARD and/or who had RA of shorter duration.

The univariate linear regression models showed that improvement in mHAQ generally was associated with baseline disease activity measures: DAS28, CDAI, SJC, TJC, and physician global assessment, i.e., those with higher baseline scores were more likely to decrease their scores. The univariate model did not show a relationship of change in mHAQ with disease duration or to the number of DMARD a patient had previously used. However, the ratio of the number of DMARD previously used divided by the disease duration (i.e., patients who switched DMARD more frequently, the DMARD frequency index) did show a relationship with change in mHAQ. The patients who changed DMARD more frequently had more improvement in their mHAQ, suggesting that although the absolute number of previous DMARD was not a factor in response to a new DMARD, the frequency with which DMARD are changed is associated with a better clinical outcome. This is supported by the significant relationship between improvement in mHAQ and the addition or discontinuation of a DMARD during the 6–12 months following the introduction of a new DMARD.

Our multivariate linear regression models (not including the ratio of DMARD previously used to disease duration) accounted for more variables and their interrelationships. The DMARD frequency index, the addition of another DMARD during followup, and higher baseline mHAQ predicted improvement of mHAQ. Repeating the model evaluating disease duration also showed similar results. Again, however, there was no relationship of mHAQ response to the number of DMARD previously used.

Our study confirms the published clinical trial literature regarding the relationship of disease duration with response to the next DMARD in community-dwelling patients across the country. In 2000, Anderson *et al* performed a meta-analysis of 14 clinical trials (1985–1998) to evaluate factors predicting response to therapy in RA; 11 were methotrexate (MTX) trials[4]. There was a wide range of mean disease duration across the trials (0.5 to 17.5 yrs). Tender/swollen joint count, ESR, patient severity, physician severity, HAQ-DI, and pain measures improved less in patients with longer duration of disease. Aletaha and Ward, in a metaanalysis using 36 clinical trials, found that HAQ-DI scores were higher with longer duration of RA, and suggested that less improvement in HAQ may be seen in patients with longer disease duration[3].

Regarding the effect of prior DMARD on the response to subsequent DMARD, Hurst, *et al*[8] and Fries, *et al*[11] state that the order in which DMARD are received by the patient is important in determining response. Aletaha and Smolen[10] showed that the first DMARD employed was continued longer by patients and was more effective, compared to subsequent drugs used. Kapral, *et al*[12] showed that 86 patients rechallenged with low-dose MTX improved and continued the medication, but others, having used other DMARD, did not improve when rechallenged with those other DMARD. These data, while interesting, do not directly address the question of lesser responses as more DMARD are used.

An evaluation of the relationship of rate of change of DMARD (ratio of number of previous DMARD to disease duration in years) with mHAQ response has not been reported. Our finding regarding the rate of change of DMARD in real-life patients with RA supports the view that DMARD should be changed frequently if response is not achieved, and supports the evolving concept of goal-oriented DMARD management, in which DMARD treatment is changed if the patient has not reached a targeted response (e.g., DAS < 2.6) by a certain time (e.g., within 3–4 months). We did not perform extensive subgroup analyses, thus it is possible that the DMARD frequency index is not predictive of mHAQ improvement in all types of patient subgroups. This result requires further validation, but the rate of DMARD change may provide a marker of treatment intensity.

Our study showed no effect of the number of previously used DMARD on subsequent response. Our results may differ from datasets that used data derived from clinical trials, which represent a more selected patient group. Our data represent a large number of patients in real-world clinical practice, and probably more closely describe the general US population with RA.

Our study has some limitations. The prospective observational CORRONA database was not specifically designed for the purpose of the study. Patients in the CORRONA

database have lower disease activity compared to other databases (low baseline mHAQ) and this may contribute to a floor effect, where the 0.3–0.4 lower baseline mHAQ scores (inherent in the instrument compared to the scores using HAQ-DI[15]) leave less room for improvement. Residual joint damage can be associated with higher mHAQ score that may not be amenable to changes in DMARD. However, clinical trials have shown that the mHAQ can detect change when evaluating the data[16], thus the mHAQ was selected as an adequate measure of quality of life in the CORRONA database. In addition, the database did not collect data on reasons for previous DMARD withdrawal, which may have been another covariate in the model for mHAQ response.

Our study shows that in the CORRONA database, higher baseline mHAQ, shorter disease duration, addition of another DMARD during followup, and the frequency of DMARD changes are associated with improvement in mHAQ when evaluating the response to a new DMARD. However, the total number of DMARD ever used does not predict improvement of the mHAQ. The frequency of change of DMARD during patients' disease duration is a relatively new way of evaluating how rapidly physicians change DMARD. These results support the view that rheumatologists should change patients' DMARD when needed to improve RA disease activity.

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