Equivalent Responses to Disease-modifying Antirheumatic Drugs Initiated at Any Time During the First 15 Months After Symptom Onset in Patients with Seropositive Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate responses by time to initiation of nonbiologic disease-modifying antirheumatic drugs (DMARD) in a DMARD-naive cohort of patients with early seropositive rheumatoid arthritis (RA).

Methods. Subjects were categorized by the time from symptom onset to the first DMARD use (median 5.7 months, range 0.6–15.9). Subjects who started their first DMARD within 5 months of symptom onset were compared to subjects who started after 5 months. Disease Activity Scores (DAS-44) and total Sharp Score (TSS) progression rates were analyzed using Wilcoxon rank-sum and chi-square tests; multiple linear regression analysis adjusted for potential covariates. The slope of the least-squares regression line was calculated to estimate the annualized TSS progression rates.

Results. Of 233 RA patients, 76% were female and mean age was 50 (SD 13) years. At DMARD start, DAS-44 was similar in all subsets within the 0.6 to 15 months' duration between symptom onset and DMARD initiation. Erosion scores tended to be higher in those who started DMARD later, but Health Assessment Questionnaire-Disability Index (HAQ-DI) scores were higher in those who started DMARD earlier. During the 2 years after DMARD initiation, improvements in HAQ-DI and DAS-44 were similar in the various duration subsets, with about 25% ever achieving DAS remission (DAS < 1.6). Radiographic progression tended to be numerically but not statistically more rapid in the earlier subsets.

Conclusion. Following initiation of nonbiologic DMARD therapy at various times within 15 months of symptom onset, improvements of DAS-44, HAQ-DI, remission rate, and radiographic progression rate were similar, although higher baseline erosion scores were present in those with later initiation of DMARD. (J Rheumatol First Release Feb 1 2010; doi:10.3899/jrheum.090818)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE ACTIVITY SCORE RADIOGRAPH REMISSION WINDOW OF OPPORTUNITY DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Rheumatoid arthritis (RA) is a symmetric inflammatory polyarthritis leading to significant loss of functional mobility and deformity, ultimately resulting in physical disability. Disease-modifying antirheumatic drugs (DMARD) decrease inflammation and slow this destructive process. However, DMARD are variable in efficacy, and only a small percentage of patients achieve long-lasting disease remission[1].

In the 1980s, the mainstay of treatment was the pyramid approach (step-up therapy approach), until a pivotal article

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in 1989 proposed that patients with RA treated early with DMARD achieved better longterm outcomes than patients treated later[2]. Eventually, the pyramid theory was discarded and new models for RA treatment emerged.

A newer paradigm, the "window of therapeutic opportunity"[3,4], as used in oncology, suggests that early treatment of a smaller mass of cancer cells is more responsive to chemotherapeutics and more likely to result in remission and cure, compared to later treatment of a larger mass of cancer cells. Aggressive treatment of RA close to its onset would equate to treating a smaller mass of destructive inflammatory cells; thus, this might be more effective in achieving remission than treatment later in the disease course when the inflammatory cell burden is increased and a self-perpetuating chronic autoimmune inflammation has developed.

Rheumatologists have had different interpretations for the window of therapeutic opportunity[3,4]. For this analysis, we define the window of therapeutic opportunity to mean that DMARD treatment closer to symptom onset should effect a substantial long-lasting change in the course of the disease, decrease the rate of radiographic progression, improve functional disability, and most importantly, result in high rates of RA remission. To some rheumatologists, however, "window" means that earlier DMARD is necessary before the window closes, so that later treatment is less effective than therapy started early, when the window is open. In this interpretation, later therapy will result in more radiographic damage and less remission than early starts[3].

We agree that earlier treatment with DMARD decreases the cumulative joint damage in RA, although few patients achieve remission. However, if the oncologic definition of the window of opportunity theory holds true, treatment of RA prior to a specific time of disease duration (i.e., the inflammatory threshold) should markedly increase the remission rate by limiting the immune system activation. Previous studies have demonstrated mixed results with regard to the "window of therapeutic opportunity" theory[5-11].

The objective of our analysis was to evaluate whether a window of therapeutic opportunity exists in a strictly defined, observational, DMARD-naive, seropositive early RA cohort treated by practicing rheumatologists before the availability of anti-tumor necrosis factor (TNF) and other biologic therapies. The entry criteria selected for RA patients fulfilling the 1987 American College of Rheumatology (ACR) criteria[12] with rheumatoid factor (RF) positivity and other characteristics associated with a poorer prognosis. The study objective was to examine whether a specific window of opportunity exists between symptom onset and initiation of DMARD during which induction of durable remission and arrest of radiographic progression is possible and more likely than with DMARD therapy initiated after such a point.

MATERIALS AND METHODS

Patients. We studied a subset of patients with early RA (within 16 months from onset of symptoms to initiation of DMARD) participating in a longterm observational study by the Western Consortium of Practicing Rheumatologists, a regional consortium of rheumatology practices in the Western United States and Mexico. The consortium of 36 rheumatology physicians participating in this subset study were from 22 community and 4 university practices in California, Idaho, New Mexico, Oregon, Utah, Colorado, Washington, and Wyoming and Guadalajara, Mexico. Patient entry into this observational cohort began in 1993.

Patients with RA according to the 1987 ACR criteria[12] were entered in this observational study if they satisfied entry criteria, as follows: ≤ 24 months of disease duration since symptom onset, no previous DMARD treatment, RF seropositivity (RF ≥ 1:80 titer, or ≥ 40 IU/ml), ≥ 6 swollen joints (out of 66), and ≥ 9 tender joints (out of 69 measured joints).

Study assessments. Assessment at study entry (baseline), 6 months, 1 year, and yearly thereafter included all the core set measures required to calculate the ACR response criteria[13] and Disease Activity Score [DAS-44; using the Ritchie index, swollen joint count of 44 joints, and erythrocyte sedimentation rate (ESR)[14,15]]. Blood specimens were collected for C-reactive protein (CRP) and Westergren ESR were determined when clinically indicated. Antibodies to cyclic citrullinated peptide (CCP) were also determined from frozen specimens for a subset of patients.

At study entry and every 6 months thereafter, patients were asked to complete a detailed self-report mailed questionnaire that included demographic, health, and pain data, and detailed medication use, as well as global visual analog scale (VAS) assessments and the Health Assessment Questionnaire-Disability Index (HAQ-DI)[16]. Patients were also asked to recall their symptom onset date (the date of first appearance of joint symptoms that led to the diagnosis of RA)[17].

Study visits included radiographs of the hands, wrists, and forefeet. Standard posteroanterior radiographs that included both hands and wrists and anteroposterior radiographs that included both forefeet were obtained at entry, 6 months, 12 months, and yearly in the rheumatologists' offices or by their local radiology facility.

Outcomes. Damage due to RA was scored by 2 experienced readers (JTS, RHG) for erosions (scale 0 to 5) and joint space narrowing (scale 0 to 4); total Sharp score (TSS) is the sum of the erosion scores (ES) and joint space narrowing scores (JSNS)[18,19]. Radiographs were read in patient sets, randomized and blinded for sequence. The reader's independent scores for each radiograph were averaged and the mean was used for the analysis.

Reliability of the readers was assessed by the intraclass correlation coefficient (ICC) and smallest detectable difference (SDD). The ICC and SDD for the average of 2 readers' scores were 0.97 and 3.07 units for ES, 0.93 and 7.52 units for JSNS, and 0.90 and 12.71 units for TSS, respectively. The progression rate was expressed as change in (total, erosion, or joint space narrowing) score per month, annualized to express progression rate per year[20-26]. For each patient, this was calculated by determining the slope of the least-squares linear regression line of all available radiographic observations. Progression rates were assumed to remain relatively constant during the observation interval.

Statistical analysis. Patients were categorized by the interval from symptom onset to first DMARD use and this analysis included patients from initiation of DMARD to second-year assessment. Four separate cutpoints for time to first DMARD were examined: 3, 4, 5, and 6 months. Each cutpoint divided the data into 2 separate subpopulations, which were then compared on the following outcome variables: ACR 20%, 50%, or 70% response; DAS-44 remission (< 1.6); change in DAS-44; HAQ-DI at 1 and 2 years; TSS progression per year; JSNS progression per year; and ES progression per year. A very early group (< 3 months) was also compared to a very late group (≥ 10 months). Less than 3 months was selected based on a previous study[9]; the very late group included a similar number of our patients with the latest initiations of DMARD. For clarity of presentation, only the 5-month cutpoint groups and the very early and very late group comparisons

are included in the publications. Data for the other cutpoint groups are available upon request from the authors.

The groups were compared using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables (for baseline outcome variables).

To assess outcome variables (DAS-44 or radiographic scores) at 1 and 2 years after study entry we used generalized linear regression models in which the outcome is regressed on time to first DMARD and baseline score of the outcome. The first set of these models included terms for time to first DMARD and the baseline scores as covariates. The second set included anti-CCP antibody positivity as a covariate to determine if adjustment for anti-CCP affected outcomes, as anti-CCP antibody positivity has been associated with greater disease activity and poorer radiographic outcomes[27-29]. The third set of models included the first DMARD as indicator variables, whether it was methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), prednisone, or a combination. To adjust for imbalances at baseline, our last set of models included variables that were statistically different between the groups at baseline.

All primary outcome analyses were performed using SAS statistical software (Release 9.1; SAS Institute Inc., Cary, NC, USA). Statistical significance was set at the 0.05 level. Because we conducted exploratory analyses for the purpose of generating hypotheses, there was no adjustment for multiple testing.

RESULTS

Of the 233 patients with RA, 77% were women and 76% were Caucasian. Mean age at disease onset was 50 years (SD 13) and mean duration of disease was 6.2 months (SD 3.3; range 0.6–14.1 months, one outlier at 20.5 months). At baseline, the patients had active disease with mean DAS-44 of 4.8 (SD 1.2), mean tender joint count (TJC) 23 (SD 13), and mean swollen joint count (SJC) 20 (SD 11). Mean HAQ-DI was 1.22 (SD 0.7) and TSS 6.0 (SD 8.2).

The months between symptom onset and DMARD initiation were distributed relatively evenly among the patients, with a median time from symptom onset and start of first DMARD of 5.7 months (range 0.6–15.9, one outlier at 20.5 months). To illustrate the distribution of time between symptom onset and start of first DMARD, a cumulative probability plot is shown in Figure 1. Patients were ranked from those with the shortest time from symptom onset to DMARD initiation to the longest time.

Radiographic progression rates during the first 2 years after DMARD initiation were available for 197 patients. Figure 2 presents TSS progression rate cumulative probability plots of 94 patients who initiated DMARD within < 5 months (i.e., < 150 days), with 103 who initiated DMARD ≥ 5 months (i.e., ≥ 150 days) after onset of symptoms. In the < 5 months group, 28 had negative progression rates, 6 had zero progression rates, and 60 had positive progression rates. In the ≥ 5 months group, 37 had negative progression rates, 5 had zero progression rates, and 60 had positive progression rates. The mean TSS progression rates are numerically higher in the < 5 months group (3.13 ± 6.49 units/year) than in the ≥ 5 months group (1.69 ± 4.43 units/year), but the differences were not statistically significant by the Wilcoxon rank-sum test ($p = 0.3$).

Table 1 presents the baseline characteristics of subsets of our cohort, using the 5-month cutpoint of time from symptom onset to first DMARD and comparing < 3 months with ≥ 10 months. No significant differences in percentage of female patients or baseline DAS-44 data were detected. Patients treated earlier were slightly older if the 3-month

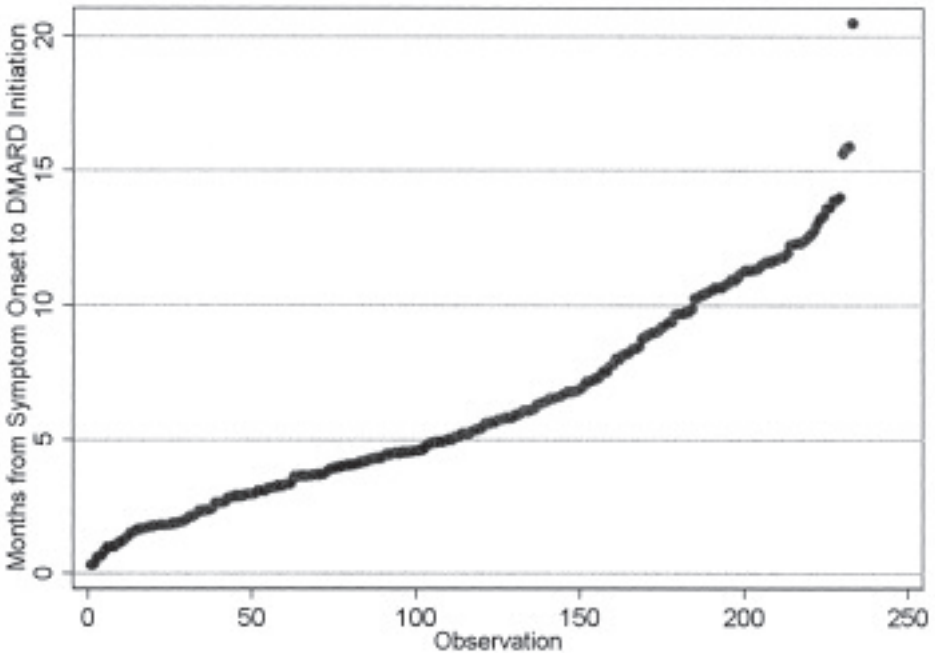

Figure 1. Cumulative probability plot: months between symptom onset and start of first DMARD. Each dot represents a single patient. Patients were ranked from those with the shortest time between symptom onset and start of DMARD to the longest time.

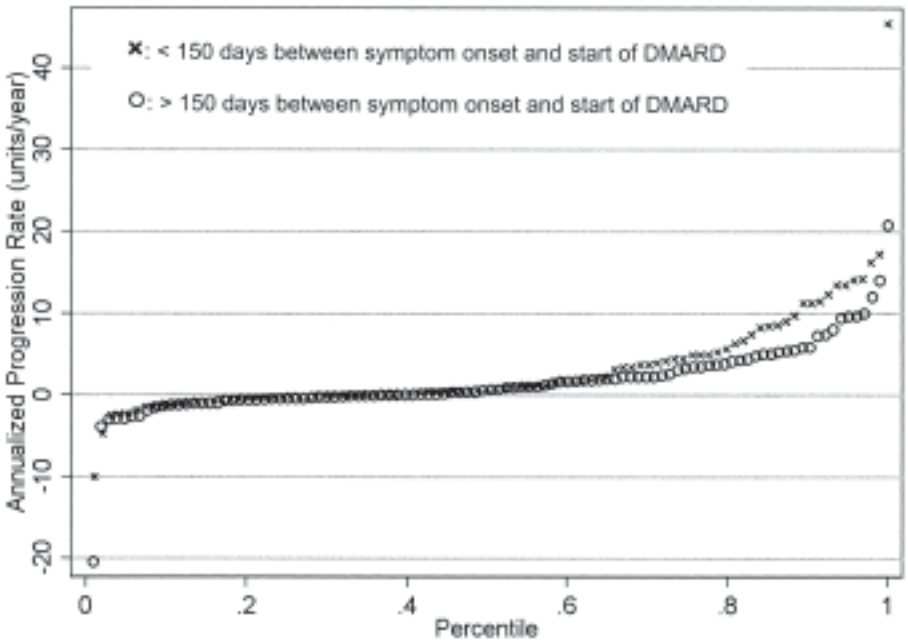

Figure 2. Cumulative probability plot of patients who had initiation of DMARD < 5 months after symptom onset compared to those who had initiation > 5 months after onset; there are no significant differences in total Sharp Score progression rates after start of DMARD treatment.

Table 1. Baseline characteristics of subject subsets using 150 day, and very early versus very late cutoff times. Data are mean (SD) unless otherwise indicated.

Characteristic	Cutpoint			
	150 Days (5 months)		Very Early	Very Late
	Early, < 150 Days	Late, ≥ 150 Days	Early, < 90 Days (< 3 mo)	Late, ≥ 300 Days (≥ 10 mo)
No. (n = 233)	110	123	51	49
Female, %	77	76	76	69
Age, yrs	51.5 (12.4)	49.4 (13.1)	53.3 (11.1)	48.1 (14.11)*
Time to first DMARD, mo	3.1 (1.3)	9.1 (3.0)	1.9 (0.7)	12.2 (1.9)
Tender joint count, 0–69	23.5 (14.3)	22.7 (12.0)	19.6 (12.5)	23.1 (13.9)
Swollen joint count, 0–66	20.0 (11.4)	19.2 (10.1)	23.4 (15.5)	20.9 (11.3)
Physician global assessment, 0–100 scale	52.5 (21.03)	47.7 (20.50)	52.3 (21.16)	48.3 (20.5)
Patient global assessment, 0–100 scale	44.3 (28.3)	43.3 (27.9)	46.3 (27.3)	45.7 (26.9)
Disease activity score (DAS-44-ESR)	4.73 (1.18)	4.76 (1.16)	4.60 (1.33)	4.92 (1.19)
Health Assessment Questionnaire, 0-3	1.35 (0.72)	1.09 (0.68)**	1.41 (0.71)	1.03 (0.56)**
Rheumatoid factor titer, IU/ml	360.44 (405.9)	389.3 (624.0)	385.3 (428.5)	399.9 (724.2)
Anti-CCP (no. positive/total), % positive	43/48 (90)	60/69 (87)	19/21 (90)	25/28 (89)
C-reactive protein, mg/dl	2.95 (3.57)	2.90 (4.01)	2.74 (3.36)	2.9 (3.79)
Erythrocyte sedimentation rate, mm/h	41.4 (23.1)	41.0 (26.3)	41.3 (24.5)	48.0 (30.4)
Erosion score	1.49 (2.18)	2.60 (4.74)	1.55 (2.45)	3.59 (4.29)**
Joint space narrowing score	3.78 (4.51)	4.07 (6.80)	4.50 (4.73)	4.94 (8.84)
Total Sharp Score	5.27 (5.69)	6.67 (9.97)	6.06 (6.43)	8.53 (12.32)

* Significantly different at $p < 0.05$, earlier versus later institution of DMARD, using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. ** Significantly different at $p < 0.01$, earlier versus later institution of DMARD, using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

cutoff of the very early versus very late comparison was used ($p < 0.05$; Table 1). The RA patients treated earlier had significantly higher baseline HAQ-DI scores compared to patients treated later ($p < 0.05$; Table 1). RA patients starting treatment later had significantly higher baseline erosion scores (Table 1) if the very early group (< 3 months) was

compared to the very late group (≥ 10 months) (ES 3.59 vs 1.55, respectively; $p < 0.01$). There were no significant baseline differences in ESR or CRP or in DAS-44 scores.

None of the earlier compared to the later DMARD initiation subgroups differed in MTX dosage or duration of use during the first 24 months after starting DMARD (Table 2). Patients who started HCQ later than 10 months took it longer than those who started earlier than 3 months (15.0 vs 9.1 months, respectively; $p < 0.05$). With the 5-month cutoff point, those who started HCQ later than 5 months were treated with a lower dose than those who started earlier (341 vs 375 mg, respectively; $p < 0.05$). Patients in the group with very late initiation of DMARD (≥ 10 months) took prednisone significantly longer compared to those in the very early group (17 vs 13 months, respectively; $p < 0.05$), but there was no significant difference in their average daily dose. The proportion of patients started on MTX or MTX combinations did not differ in their early versus later DMARD starts.

Outcomes. There were no significant differences in changes of ESR, CRP, HAQ-DI scores, or radiographic total Sharp score progression rates from baseline in any of the groups (Table 3).

At both the 1- and 2-year timepoints, there were no differences in percentage of patients achieving ACR20 or ACR50 in any of the subsets of time to start of DMARD (Table 3). There were no significant differences in the proportion of patients who achieved DAS-44 remission (< 1.6) in any group during 1- or 2-year followup. In the generalized linear models with adjustment for anti-CCP (n = 106, because not all patients had anti-CCP testing), time from symptom onset to DMARD initiation did not significantly influence outcomes like DAS-44, ES, JSNS, and TSS.

In the models adjusting time to first DMARD by baseline DAS-44, HAQ-DI, ESR, CRP, ES, and JSNS, the only outcome variables that were found to be significantly associated with time to first DMARD were ESR at 2 years ($p = 0.002$) and DAS-44 at 2 years ($p = 0.05$). Shorter time to first DMARD was associated with less improvement in ESR or DAS-44 scores within the 2 years. In the models adjusting for initial use of MTX, HCQ, SSZ, or prednisone, the time to first DMARD did not significantly influence any of the outcome measures after 1 or 2 years.

DISCUSSION

The goal of our study was to evaluate the relationship of symptom duration to initiation of DMARD in a cohort of patients with early, seropositive, moderately severe RA, and to determine whether very early and varying periods to DMARD treatment of RA can effect a major long-lasting change in functional capacity, radiographic progression rate, and DAS-44 remission[3,4]. Our observational cohort of 233 DMARD-naive patients with RF-positive RA were all early in their disease course, with time from symptom onset to DMARD initiation of 0.6 to 15.9 months. They were subdivided into categories based on the time from symptom onset to DMARD initiation using a 5-month cutpoint as well as a very early group (< 3 months) versus a very late group (≥ 10 months).

In this cohort, earlier institution of DMARD therapy did not significantly change the DAS-44 remission rate, improvement in functional disability, or radiographic progression rate compared to subjects who started DMARD later (up to 15 months after symptom onset).

At study entry, most disease measures (e.g., DAS-44, TJC, SJC, ESR, and CRP) were not significantly different

Table 2. Medication profile during the first 24 months after initiation of DMARD. Data are mean (SD) unless otherwise indicated.

	Cutpoint			
	150 Days (5 months)		Very Early vs Very Late	
	Early, < 150 Days, N = 110	Late, ≥ 150 Days, N = 123	Early, < 90 Days, N = 51	Late, ≥ 300 Days, N = 49
No. months on MTX (n = 183)	15.1 (8.1)	15.7 (7.2)	13.84 (8.24)	17.4 (7.4)
Mg/wk	13.2 (8.4)	12.3 (6.1)	14.88 (11.78)	13.5 (6.7)
n (%)	93 (84.5)	90 (73.2)	40 (78.4)	33 (67.3)
No. of months on HCQ (n = 182)	11.0 (8.5)	14.3 (8.0)	9.14 (8.05)	15.0 (8.4)*
mg/day	374.6 (109.9)	340.9 (102.3)*	362.37 (143.0)	312.8 (87.6)
n (%)	43 (39.1)	65 (52.8)	21 (41.2)	26 (53.1)
No. months on prednisone (n = 147)	14.1 (8.1)	14.6 (8.7)	12.78 (7.33)	17.15 (7.2)*
Mg/day	6.5 (3.0)	6.29 (3.7)	6.62 (2.72)	5.4 (2.3)
n (%)	73 (66.4)	74 (60.2)	31 (60.8)	27 (55.1)
No. months on SSZ (n = 50)	13.0 (8.6)	11.8 (7.9)	16.36 (7.62)	9.5 (8.5)
Mg/day	1845.5 (735.3)	1742.3 (587.7)	1763.30 (646.0)	1835.0 (660.3)
n (%)	26 (23.6)	24 (19.5)	14 (27.5)	10 (20.4)
MTX+HCQ, no. patients (%)	12 (10.9)	13 (10.6)	5 (9.8)	5 (10.2)
MTX+PRED, no. patients (%)	25 (22.7)	21 (17.0)	10 (19.6)	8 (16.3)

* Significantly different at $p < 0.05$, earlier versus later institution of DMARD, using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

Table 3. One and 2-year followup outcomes.

Outcome	Cutpoint: 150 Days Early, < 150 Days	150 Days Late, ≥ 1150 Days	Very Early Early, < 90 Days	Very Late Late, ≥ 300 Days
% meeting ACR20 1 yr (n = 165)	50	42	42	39
% ACR20 2 yrs (n = 125)	55	48	48	40
% ACR50 1 yr	24	27	28	29
% ACR50 2 yrs	36	29	28	23
% ACR70 1 yr	11	13	6	13
% ACR70 2 yrs	27	14	16	17
% 1 yr ever DAS-44 < 1.6	19	14	16	15
% 2 yr ever DAS-44 < 1.6	25	25	22	21
Mean (SD) Change from Baseline				
1 yr DAS-44 (n = 153)	–1.75 (1.55)	–1.61 (1.52)	–1.83 (1.53)	–1.74 (1.80)
2 yr DAS-44 (n = 120)	–1.96 (1.49)	–1.85 (1.45)	–1.90 (1.60)	–1.74 (1.56)
1 yr HAQ-DI (n = 179)	–0.59 (0.66)	–0.45 (0.58)	–0.55 (0.77)	–0.41 (0.56)
2 yr HAQ-DI (n = 161)	–0.61 (0.57)	–0.42 (0.68)	–0.63 (0.58)	–0.35 (0.61)
1 yr CRP (n = 187)	–0.97 (3.27)	–0.98 (7.00)	–0.91 (2.59)	–1.89 (3.74)
2 yr CRP (n = 144)	–1.70 (3.59)	–0.89 (4.53)	–0.90 (2.36)	–1.12 (3.62)
1 yr ESR (n = 187)	–13.4 (25.14)	–12.6 (26.64)	–14.9 (26.99)	–18.03 (26.54)
2 yr ESR (n = 144)	–16.4 (26.40)	–10.96 (28.51)	–13.3 (28.81)	–17.00 (31.05)
2 yr ES, units per yr (n = 197)	1.70 (2.92)	1.04 (2.78)	2.36 (3.39)	1.14 (2.05)
2 yr JSNS, units per yr (n = 197)	1.47 (4.65)	0.72 (2.49)	2.16 (6.42)	0.63 (1.37)
2 yr TSS, units per yr (n = 197)	3.13 (6.49)	1.69 (4.43)	4.62 (8.46)	1.77 (2.75)

Outcomes are adjusted for time to first disease-modifying antirheumatic drug and the baseline scores as covariates. Progression rates for erosion scores (ES), joint space narrowing scores (JSNS), and Total Sharp Score (TSS) are expressed as units per year. Comparison of proportions was done with chi-square tests of association, Fisher's exact tests. Change scores from baseline were compared using Wilcoxon rank-sum tests.

when compared in subsets created by dividing the cohort at various timepoints from symptom onset to DMARD initiation. However, comparing the very early < 3 months with the very late ≥ 10 months subsets, the very early subset was 5 years older and had poorer physical function (HAQ-DI 1.41 vs 1.03, respectively). Indeed, all subgroup comparisons demonstrated higher baseline HAQ-DI in the earlier groups, suggesting that those with more functional impairment may have sought a rheumatologist sooner. This may result in confounding by indication bias, in which those patients with more symptomatic disease saw a rheumatologist sooner and received earlier and more aggressive treatment. Treatment of more symptomatic patients earlier could lead to similar or improved outcomes, compared to those with more indolent disease who sought care later[30]. However, in our cohort the selection of a specific DMARD treatment was not more aggressive for those patients who started DMARD earlier compared to those who started later (Table 2). One way to adjust for this bias is to use propensity score analysis[31,32], but since only a few variables are different at baseline, we chose to adjust for them by adding them to our generalized linear models. Adjusting for these baseline differences did not significantly affect the outcomes.

Of note, patients who started a DMARD later had higher ES at baseline, suggesting that they had more time to accumulate damage prior to initiation of DMARD. Following DMARD initiation, at 1- and 2-year followup, despite earlier treatment, the earlier treatment groups demonstrated no clear difference in therapeutic response in terms of ACR50 or ACR70 response, or DAS-44 < 1.6 remission, or change from baseline in DAS-44, HAQ-DI, CRP or ESR, or in Sharp score progression rates.

Strengths of our study include our homogeneous study population: (1) subjects with early RA with disease duration assessed from the symptom onset and not from the referral-dependent time of diagnosis by a physician; (2) all subjects had active seropositive RA (with positive RF ≥ 40 IU/ml) with a mean TJC of 23 and SJC 20 (minimum TJC 9 and SJC 6) when they entered the study (note that these findings should not be applied to patients with seronegative RA and undifferentiated polyarthritis, who are more likely to have spontaneous remission and were not included in the study); and (3) all patients were treated by practicing rheumatologists, and the findings are representative of those attained in routine clinical practice.

Limitations include that our study was not designed specifically to answer the proposed question and the lack of control over choice of DMARD. Perhaps certain DMARD, biologic agents, or combinations can eliminate the inflammatory cell burden during the postulated "window" and thus the choice of DMARD could influence whether a window of opportunity is detected. The problem of confounding by indication includes situations where patients may have initiated certain DMARD, depending on the status of their RA[30].

However, in our cohort, the proportion of patients starting MTX or MTX combinations did not differ in the early versus the later DMARD starts.

We cannot rule out that patients who started DMARD therapy later than 15 months from symptom onset would have had markedly poorer responses; however, we could not detect major duration-dependent differences in outcomes within the range of times that we tested. The cohort included only one patient who started DMARD 20 months after symptom onset, but there were no other subjects after 15 months, and inferences beyond 15 months are not possible. We did not test the possibility that DMARD treatment during a window of opportunity in "pre-RA" (prior to fulfilling the ACR criteria) or asymptomatic genetically predisposed persons with RF and/or anti-CCP antibodies could prevent the eventual expression of clinical RA.

There may be a complex interaction between choice of DMARD and their early initiation that is optimal for the treatment of RA, but we did not observe a "window of therapeutic opportunity" within which initiation of DMARD in active seropositive early RA induced durable and complete remission, with normalization of laboratory measures, as well as clinical and radiographic outcomes used in this study. A well designed controlled clinical trial randomizing patients with early RA to either early or late treatment is the ideal way to answer this question, but it is no longer ethical to randomly withhold treatment in order to prove that more joint damage occurs in one group. We believe that early initiation of DMARD is of proven clinical benefit to patients with RA to prevent or decrease the accumulation of irreversible joint damage regardless of duration of symptoms[33-35].

In terms of clinical implications, inability to demonstrate an oncologic (curative) window of opportunity in our cohort does not mean that initiation of DMARD can be delayed without consequences. Substantial joint damage was present at baseline in all the disease-duration subgroups; even those with < 3 months' disease duration had a mean total Sharp score of 6.06. Presumably irreversible joint damage accumulates during the interim before initiation of DMARD, and the subset of our cohort who initiated DMARD very late after symptom onset had significantly higher baseline erosion scores than those starting DMARD very early (Table 1). Biologic agents (i.e., TNF inhibitors) were not available when this cohort was treated, but several large clinical trials in patients with a wide range of disease durations have demonstrated that anti-TNF agents in combination with MTX are more likely to arrest radiographic progression than MTX alone[33-35]. If the currently available anti-TNF/MTX combinations are started early enough, this pre-DMARD joint damage might be avoidable.

However, during the 2 years after starting DMARD (up to 15 months after symptom onset), the rate of progression of joint damage was not less in those with a shorter interval between symptom onset and DMARD initiation. Indeed, ES and TSS progression rates were numerically higher in the subsets that started DMARD earlier, supporting the assumption that channeling bias caused patients with more severe early RA to seek earlier rheumatologic care. This finding is contrary to what one would expect if a limited early window of therapeutic opportunity was associated with markedly better disease control.

Thus, in our observational cohort, we did not detect a "window of therapeutic opportunity" that could achieve the sought-after goal of curative ablation of the inflammatory cell mass. However, despite the absence of a window, we advocate that effective DMARD therapy should be initiated as soon as possible to minimize cumulative damage in patients with early aggressive RA.

APPENDIX. The Western Consortium of Practicing Rheumatologists: J. Javier Orozco-Alcala, MD (Guadalajara, Mexico); Karen Basin, MD (Medford, OR); Martin Berry, MD (Bakersfield, CA); Charles Boniske, MD (Visalia, CA); Melvin Britton, MD (Palo Alto, CA); Ken Bulpitt, MD (Torrance, CA); Jeffrey Carlin, MD (Seattle, WA); H. Walter Emori, MD (Medford, OR); Robert Ettlinger, MD (Tacoma, WA); Daniel Furst, MD (Seattle, WA, now in Los Angeles, CA); Gregory Gardner, MD (Seattle, WA); Robert Gerber, MD (Medford, OR); Maria Greenwald, MD (Palm Desert, CA); Karen Kolba, MD (Santa Maria, CA); George Krick, MD (Tacoma, WA); Max Lundberg, MD (Sandy, UT); Anne MacGuire, MD (Casper, WY); Philip Mease, MD (Seattle, WA); Ghislaine Bernard Medina, MD (Guadalajara, Mexico); Raymond Mirise, MD (Los Angeles, CA, now in Glendale, AZ); Ina Oppliger, MD (Seattle, WA, now in Kansas City, MO); Allen Sawitzke, MD (Salt Lake City, UT); Gerald Schoepflin, MD (Portland, OR); John Seaman, MD (Seattle, WA, now in Tacoma, WA); Robert Shapiro, MD (Sacramento, CA); Fredrica Smith, MD (Los Alamos, CA); Marcia Sparling, MD (Vancouver, WA); Elizabeth Tindall, MD (Portland, OR); Michael Weisman, MD (San Diego, CA, now in Los Angeles, CA); Mark Wener, MD (Seattle, WA); Craig Wiesenhutter, MD (Coeur d'Alene, ID); Kenneth Wiesner, MD (Sacramento, CA); Robert Willkens, MD (Seattle, WA); Kenneth Wilske, MD (Seattle, WA); Andrew Wong, MD (Northridge, CA); George Young, MD (Boulder, CO).

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