Patient, Disease, and Therapy-Related Factors That Influence Discontinuation of Disease-Modifying Antirheumatic Drugs: A Population-Based Incidence Cohort of Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** A major challenge in management of rheumatoid arthritis (RA) is prediction of longterm response to disease-modifying antirheumatic drug (DMARD) treatment. Our objective was to identify the predictors of DMARD discontinuation in an incidence cohort of patients with RA followed continuously from their incidence date.

Methods. Members of a population-based incidence cohort of Rochester, Minnesota, residents aged ≥ 18 years diagnosed with RA (by 1987 American College of Rheumatology criteria) from January 1, 1955, to January 1, 1995, were followed longitudinally through their complete medical records until January 1, 2001. Detailed drug exposure data were collected on all DMARD and glucocorticoid regimens. Subjects were considered exposed to a DMARD if duration of use was ≥ 30 days. Time to discontinuation of DMARD was estimated using survival analysis techniques. Andersen-Gill models with multiple events per patient were used to assess the influence of demographics, calendar time, comorbidities, disease characteristics [disease duration, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), joint counts, radiographic changes, nodules, RA complications], and therapy characteristics (DMARD use, singly or in combination, glucocorticoid use, first or subsequent regimen, effect of previous therapy) on time from DMARD initiation to discontinuation.

Results. The study population comprised 345 DMARD-treated patients (73% female) with mean age of 53.1 years and mean followup 15.4 years. Median time taking any DMARD was 16.0 months for the first, and 17.9 months for all regimens. Methotrexate (MTX) had the longest time to discontinuation, with a median of 30.3 months without folate, and 61.7 months with folate supplementation. Among the various disease characteristics examined, only higher ESR at DMARD initiation was significantly associated with a shorter time taking DMARD [hazard ratio (HR) 1.05 per 10 mm/h increase, 95% CI 1.02, 1.08]. In multivariable Andersen-Gill models considering all DMARD regimens, hydroxychloroquine use (HR 0.77, 95% CI 0.64, 0.92) and MTX use (HR with folate 0.39, 95% CI 0.30, 0.51; HR without folate 0.51, 95% CI 0.39, 0.67) were significantly associated with longer time to DMARD discontinuation, whereas prior MTX use (HR 1.96, 95% CI 1.57, 2.45) was associated with shorter time to DMARD discontinuation, after adjusting for age, sex, calendar year, Charlson comorbidity index, disease duration, and ESR at DMARD initiation. Disease duration was negatively associated with time to DMARD discontinuation; each 10 year increase in disease duration corresponded to a 14% decrease in the risk of discontinuation (HR 0.86, 95% CI 0.75, 0.98).

Conclusion. Longer RA disease duration does not appear to increase the risk of DMARD discontinuation. However, high disease activity (as assessed by ESR) is associated with a higher likelihood of discontinuing DMARD. MTX failure may identify a subgroup of patients who are less likely to respond to other DMARD and therefore could be considered as candidates for biological therapies. (J Rheumatol 2006;33:248–55)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE-MODIFYING ANTIRHEUMATIC DRUGS
DISCONTINUATION DRUG RESISTANCE DRUG RESPONSE

Current management of rheumatoid arthritis (RA) is characterized by early initiation and sequential regimens of disease-modifying antirheumatic drugs (DMARD) along with nonsteroidal antiinflammatory drugs (NSAID) and gluco-

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corticoids[1-3]. DMARD not only improve pain and disability, but can also modify the disease process by slowing the progression of joint destruction[3]. However, despite the encouraging efficacy findings from clinical trials, observational studies indicate that the majority of DMARD regimens are discontinued within 2–3 years[4-34]. Similarly, although the advent of biologics has been a major advance in the treatment of RA, some patients still fail to respond to these therapies[35,36]. Failure to respond to therapy, especially in the long term, is a very important problem in the clinic because it complicates efforts to manage disease activity and modify the progression of the disease[1]. Unfortunately, it is almost impossible to predict differences in response to DMARD therapy early on, so that therapy can be individualized[3,37,38]. This issue is acknowledged as one of the most important challenges in caring for patients with RA[3].

Interindividual variability in response to DMARD therapy is likely to be mediated by complex interactions between various patient, disease, and therapy characteristics in genetically susceptible individuals[38]. Moreover, there appears to be a group of patients who experience loss of drug efficacy over time[32]. Whether this is a DMARD-related phenomenon, with variability dependent on the DMARD used, or a disease-related phenomenon, with variability dependent on disease severity and disease duration, remains unknown[39]. Future advances in pharmacogenetics are likely to improve prediction of response to DMARD therapy substantially, but until then, a better understanding of the patient, disease, and therapy-related predictors of response to DMARD therapy are urgently needed[3,38,40,41]. Our aim was to identify predictors of DMARD discontinuation over a 45-year period in a population-based incidence cohort of patients with RA.

MATERIALS AND METHODS

Study setting. Epidemiological research in Rochester, Minnesota, is possible because the city is relatively isolated from other urban centers, and nearly all medical care is delivered to local residents by a small number of providers. A medical records linkage system allows easy access to complete records from all healthcare providers for the local population including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and the few private practitioners. Thus, the details of every inpatient and outpatient encounter, laboratory results, pathology reports, and correspondence concerning each patient can easily be accessed. The potential of this system for population-based research has been described[42-45]. The long, continuous, and comprehensive followup provided by this record linkage system constitutes a unique opportunity to study therapeutic trends in a geographically defined nonreferred RA population.

Study population. Using this resource, a population-based incidence cohort of all cases of RA first diagnosed between January 1, 1955, and January 1, 1995, among Rochester residents ≥ 18 years of age was assembled, as described[45-47]. All cases fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA[48]. Incidence date was defined as the first date of fulfillment of 4 of the 7 diagnostic criteria. All cases were followed longitudinally through their complete (inpatient, outpatient) medical records beginning at age 18 (or date of migration to Olmsted County for those who first became residents after age 18) and continuing until death, migration from Olmsted County, or January 1, 2001. The study population is limited to the 345 patients who received at least one DMARD regimen during followup.

Data collection. Data, including detailed information on comorbidities, RA disease characteristics, and use of DMARD and glucocorticoids, were collected from the resources described, by 4 nurse abstractors according to a prespecified and pretested protocol. Before starting data analysis, extensive checks for data consistency, proper sequences of dates, and missing or incomplete data were performed. Where necessary, medical records were reviewed again, and questions were resolved by consensus of the investigative team.

Selected comorbid conditions, including peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, ulcers, malignancies, renal disease, liver disease, and history of alcoholism, were ascertained through review of the medical records and classified using the Charlson comorbidity index[49]. RA disease activity and severity characteristics were assessed both at baseline (RA incidence date) and throughout followup, and included rheumatoid factor (RF) positivity (titer ≥ 1:40), erythrocyte sedimentation rate (ESR), tender and/or swollen joint counts, rheumatoid nodules, RA complications and erosions, periarticular osteoporosis, and destructive changes on radiographs. ESR at RA incidence date (disease onset) was defined as the highest recorded ESR during the first year after RA incidence date. Joint tenderness and/or swelling were assessed during the first year after RA incidence date (disease onset) and throughout followup, and were categorized as small joint involvement (including wrists, ankles, metacarpophalangeal, metatarsophalangeal, distal interphalangeal, and/or proximal interphalangeal joints of the hand and foot) and large joint involvement (including the elbow, shoulder, hip, and knee joints). RA complications included rheumatoid lung disease (i.e., pulmonary vasculitis, intrapulmonary rheumatoid nodules, Caplan's syndrome, chronic pleuritis, interstitial pneumonitis and fibrosis, bronchiolitis), vasculitis (i.e., various forms of vasculitis, arteritis, vasculopathy, mononeuritis multiplex), Felty's syndrome, Sjögren's syndrome, rheumatoid myocarditis, and others (e.g., scleritis, episcleritis, uveitis, bronchiolitis obliterans).

For each DMARD regimen, details were collected on drug name, starting and stopping dates, and duration of use. If it was not clear when a DMARD was stopped, treatment was assumed to have been stopped midway between the last date that the patient was definitely on the treatment and the first date the patient was definitely off the treatment. Subjects were considered exposed to a DMARD if duration of use was ≥ 30 days. The following DMARD were considered: intramuscular (IM) and oral (PO) gold, sulfasalazine (SSZ), hydroxychloroquine (HCQ), azathioprine (AZA), D-penicillamine (D-Pen), methotrexate (MTX), leflunomide, etanercept, infliximab, cyclosporin A, immunosuppressants, and alkylating agents. Starting and stopping dates were collected for each folic or folinic acid supplementation. For all glucocorticoid regimens, data were collected on drug name, route of administration, starting and stopping dates, duration of use, and dosages.

Concomitant therapy was defined as 2 DMARD started within 30 days of one another. An additional DMARD started more than 30 days after the initial DMARD was considered as a 30-day regimen of a single DMARD therapy followed by initiation of concomitant therapy.

Statistical methods. Baseline characteristics of the study population and changes in use of DMARD over time were summarized using descriptive statistics. Time to DMARD discontinuation was estimated using the Kaplan-Meier product-limit life table method and the log-rank test was used to test for differences between DMARD. Andersen-Gill models with multiple events per patient[50] were used to assess the influence of calendar year, demographics, comorbidities, and disease and therapy characteristics on time to DMARD discontinuation. Patients were considered at risk for DMARD discontinuation only when they were taking DMARD. In these models, DMARD duration was used as the time scale, where patients started at time zero for each DMARD regimen and were followed until DMARD discontinuation, death, or date of last followup. Patients who

were still taking DMARD at last followup or at death were censored. Disease and therapy characteristics at RA incidence date as well as at DMARD initiation date were assessed. Comorbidities, measured throughout followup, were modeled as time-dependent covariates to assess their influence on DMARD discontinuation, since an individual without a comorbid condition at the start of analysis could develop it during followup. A stepwise process was used to develop a multivariable model. All disease and therapy-related variables (in Tables 3 and 4) were considered for inclusion in the multivariable models, and those with p values less than 0.05 were retained. Age, sex, calendar year of DMARD initiation, and disease duration were included as adjustors in the multivariable model. All 2-way interactions among significant main effects were examined.

RESULTS

The study population of 345 RA patients with a history of DMARD use had a mean age of 53.1 years at RA incidence date and 251 (72.8%) were female. Table 1 shows the characteristics of the study population at RA incidence date and over the mean 15.4 years of followup. Within the first year of RA incidence date, 216 (62.6%) patients were treated with DMARD and 102 (29.6%) patients received glucocorticoids. During the entire followup period, 240 patients (69.6%) received glucocorticoids. About 65% of the study population received more than one DMARD regimen.

These 345 patients received a total of 897 DMARD regimens over the entire followup period. The median treatment time was 16.0 months [interquartile range (IQR) 5.7, 46.7] on the first DMARD regimen, and 17.9 months (IQR 6.1, 49.0) on all regimens (Table 2). Median time taking MTX was substantially longer than for the other DMARD, irrespective of the DMARD sequence. Median time taking MTX with and without folate supplementation was 61.7 (IQR 18.8, 114.4) and 30.3 months (IQR 11.2, 84.5), respectively, for all regimens. HCQ was the next longest DMARD, with a median 18.0 months (IQR 6.2, 44.3) to discontinuation (Table 2).

The same pattern is illustrated in Figure 1. Patients continued taking MTX significantly longer than other DMARD ($p < 0.0001$). By the end of 2 years after the initiation of therapy, only 34% of the MTX regimens were discontinued,

Table 1. Characteristics of 345 subjects with RA who received at least one disease-modifying antirheumatic drug.

Characteristics	At RA Incidence Date		Ever	
	Observed, N*	N (%)**	Observed, N*	N (%)**
Age, mean (SD), yrs	345	53.1 (± 13.7)		—
Female, n	345	251 (72.8)		—
Length of followup, mean (SD), yrs			345	15.4 (± 9.3)
Charlson comorbidity score	345		345	
None		244 (70.7)		84 (24.3)
1		57 (16.5)		82 (23.8)
2		27 (7.8)		68 (19.7)
3+		17 (4.9)		111 (32.2)
RA disease characteristics				
Rheumatoid factor positive	300	198 (66.0)	336	266 (79.2)
ESR	331	43.3 (± 29.7)***	345	105 (30.4)***
Joint swelling				
Small joints	325	308 (94.8)	345	342 (99.1)
Large joints	320	137 (42.8)	345	315 (91.3)
Radiographic changes				
Destructive changes	259	46 (17.8)	317	166 (52.4)
Erosions	259	15 (5.8)	317	70 (22.1)
Periarticular osteoporosis	259	13 (5.0)	317	38 (12.0)
Rheumatoid nodules	345	21 (6.1)	345	148 (42.9)
RA complications†	345	0 (0.0)	345	103 (29.9)
RA vasculitis	345	0 (0.0)	345	14 (4.1)
RA lung disease	345	0 (0.0)	345	18 (5.2)
Medication use				
DMARD (≥ 30 days)	345	216 (62.6)††	345	
1 regimen				121 (35.1)
2 regimens				86 (24.9)
≥ 3 regimens				138 (40.0)
Glucocorticoids	345	102 (29.6)††	345	240 (69.6)

* Observed refers to the number of patients in whom the variable was measured. ** No. (%) unless noted. *** Value at RA incidence date refers to the mean (± SD) of highest recorded ESR value in first year after RA incidence date. Value in "Ever" column refers to no. (%) of patients with ≥ 3 recorded ESR values ≥ 60 mm/h. † Includes complications such as rheumatoid lung disease, vasculitis, Felty's syndrome, Sjögren's syndrome, rheumatoid myocarditis. †† Use during the first year following incidence date. ESR: erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drug.

Table 2. Median time and interquartile range (IQR) on disease-modifying antirheumatic therapy (DMARD) among 345 DMARD-treated patients who received a total of 897 regimens.

DMARD	First Regimen		All Regimens	
	No. of Regimens	Median Months (IQR)	No. of Regimens	Median Months (IQR)
Methotrexate	24	53.6 (16.8, 97.8)	176	48.8 (15.9, 109.3)
Without folate	9	19.1 (9.2, 60.9)	73	30.3 (11.2, 84.5)
With folate	15	83.0 (22.4, 110.5)	103	61.7 (18.8, 114.4)
Hydroxychloroquine	179	16.0 (6.0, 37.9)	283	18.0 (6.2, 44.3)
PO/IM gold	115	11.2 (4.0, 41.4)	231	12.9 (4.8, 41.4)
Sulfasalazine	11	21.3 (6.0, 63.5)	51	7.7 (4.0, 25.7)
D-penicillamine	14	7.3 (4.7, 11.7)	58	10.2 (5.4, 26.7)
Azathioprine	3	*	36	13.9 (5.8, 32.0)
Leflunomide, etanercept, infliximab	0		51	9.5 (3.0, 23.7)
Others*	2	*	11	6.2 (2.1, 9.9)
Total DMARD	348	16.0 (5.7, 46.7)	897	17.9 (6.1, 49.0)

* Too few numbers.

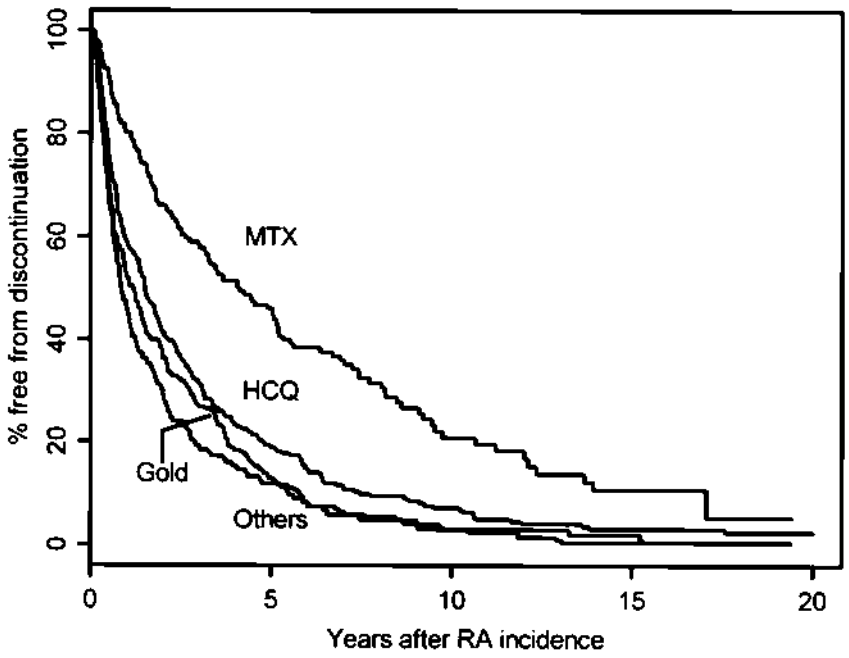

Figure 1. Time to DMARD discontinuation among 345 patients who received at least one DMARD regimen (total 897 regimens).

whereas 60% or more of the other regimens were discontinued by then. Roughly 46% of MTX regimens were still continued, without interruption, 5 years after RA incidence date.

Univariate models were used to assess the influence of age, sex, calendar year, comorbidities, and various RA disease characteristics on the time to discontinuation of DMARD (Table 3). Sex and age at RA incidence date were not significantly associated with the risk of DMARD discontinuation. Risk of DMARD discontinuation was higher in earlier calendar years (13% higher for each 10-year decrease in calendar time). The Charlson comorbidity index was a significant predictor, where each additional comorbidity index unit increased the hazard of discontinuation by 6% [hazard ratio (HR) 1.06, 95% CI 1.00, 1.12]. Of the various comorbidities, only dementia was associated with a significant increase in the hazard of discontinuation (HR 1.61, 95% CI 1.19, 2.17).

We then assessed several disease characteristics as predictors of discontinuation (Table 3). Among the various disease characteristics, only higher ESR at DMARD initiation was significantly associated with early discontinuation, with each 10 mm/h increase in ESR corresponding to a 5% increase in the risk of discontinuation (HR 1.05, 95% CI 1.02, 1.08). Similarly, patients with high ESR during the

Table 3. Univariable predictors of time to disease-modifying antirheumatic drug (DMARD) discontinuation among 345 patients with RA who received at least one DMARD regimen.

Characteristics	Univariable Hazard Ratio (95% CI)*
Age (per 10 years increase)	1.01 (0.95, 1.07)
Sex	1.02 (0.87, 1.21)
Calendar year (per 10 years decrease)	1.13 (1.05, 1.21)
Comorbidities	
Charlson Comorbidity index	1.06 (1.00, 1.12)
Dementia	1.61 (1.19, 2.17)
Rheumatoid factor-positive	1.10 (0.91, 1.34)
ESR at DMARD initiation (per 10 mm/h)	1.05 (1.02, 1.08)
ESR during first year following incidence (per 10 mm/h)	1.06 (1.03, 1.10)
Joint swelling	
Small joints	1.05 (0.79, 1.38)
Large joints	1.03 (0.88, 1.21)
Radiographic changes	
Destructive changes	0.86 (0.73, 1.01)
Erosions	0.94 (0.77, 1.16)
Periarticular osteoporosis	1.04 (0.72, 1.51)
Rheumatoid nodules	1.04 (0.89, 1.22)
RA complications†	0.98 (0.81, 1.20)
RA vasculitis	1.34 (0.84, 2.16)
RA lung disease	0.98 (0.53, 1.82)
RA disease duration (per 10 years increase)	0.91 (0.82, 1.02)

* From univariate Andersen-Gill models. † Includes complications such as rheumatoid lung disease, vasculitis, Felty's syndrome, Sjögren's syndrome, rheumatoid myocarditis.

first year of RA were significantly more likely to discontinue subsequent DMARD regimens (HR 1.06, 95% CI 1.03, 1.10). No significant associations were observed with RF positivity, presence of joint swelling, radiographic changes, rheumatoid nodules, and disease complications (Table 3).

We then examined various treatment characteristics and the likelihood of discontinuation (Table 4). First-year DMARD use, first versus subsequent DMARD, the number of previous DMARD regimens, or concomitant DMARD use had no significant effect on the likelihood of discontinuation. When compared with all other DMARD, the likelihood of discontinuation was 28% less (HR 0.72, 95% CI 0.59, 0.87) if the DMARD was HCQ, 44% less (HR 0.56, 95% CI 0.43, 0.72) if it was MTX without folate, and 61% less (HR 0.39, 95% CI 0.30, 0.49) if it was MTX with folate supplementation (Table 4). Further, patients who had discontinued MTX were almost twice as likely to discontinue subsequent DMARD than patients who had never received MTX (HR 1.89, 95% CI 1.52, 2.34). Current or prior glucocorticoid use was not associated with DMARD discontinuation, but use during the first year was associated with a higher likelihood of discontinuation (HR 1.23, 95% CI 1.04, 1.47; Table 4). These results indicate that patients with longstanding disease and with several previous DMARD regimens (other than MTX) had the same likelihood of continuing a DMARD as newly diagnosed patients. However, patients who failed MTX, and those treated with glucorticoids in the first year of RA, were more likely to discontinue subsequent DMARD, irrespective of the duration of disease or the number of previous DMARD regimens.

In a multivariable model adjusting for age, sex, calendar year, ESR, disease duration, and the number of comorbidities (at DMARD initiation), the likelihood of discontinuing a DMARD regimen was significantly lower when the DMARD was either HCQ (HR 0.77, 95% CI 0.64, 0.92) or MTX, especially with folate supplementation (HR 0.39, 95% CI 0.30, 0.51) compared with other DMARD, but was significantly higher if a prior MTX regimen (HR 1.96, 95% CI 1.57, 2.45) had failed (Table 4). These estimates were adjusted for disease duration and calendar year, indicating that the likelihood of continuing MTX remains the same irrespective of when it is initiated. These results suggest that, for example, a MTX-naive patient with long-standing RA has the same likelihood of continuing MTX as a newly diagnosed patient, all else being equal. Further, although disease duration was not significant univariately (HR 0.91, 95% CI 0.82, 1.02; Table 3), in this multivariable model, it became statistically significant; each 10-year increase in disease duration corresponded to a 14% decrease in the risk of discontinuation (HR 0.86, 95% CI 0.75, 0.98).

DISCUSSION

We describe the patterns and predictors of DMARD discontinuation in a population-based inception cohort of patients with RA ascertained between 1955 and 1995 and followed for roughly 15 years after their RA incidence date. Our findings indicate that there are significant treatment duration differences among the various DMARD. Patients continued taking MTX and HCQ significantly longer than other DMARD. MTX failure was associated with almost twice the likelihood of discontinuation, whereas use of multiple previous DMARD (except MTX) had no statistically significant effect on the likelihood of DMARD discontinuation. High disease activity (as assessed by ESR), both at disease onset and at DMARD initiation, was associated with a higher likelihood of discontinuing DMARD. Importantly, long disease duration did not increase, but instead tended to decrease the likelihood of DMARD discontinuation, once calendar year, ESR, comorbidities, and the type of DMARD were taken into account.

Given the chronic expression of RA and its significant impact on quality of life and survival, longterm treatment with DMARD is essential for sustained suppression of disease activity, and consequently, the delay of longterm complications[3]. Moreover, DMARD continuation rates are in general regarded as a surrogate for drug effectiveness and tolerability[51]. Over the last decade, various investigators examined DMARD discontinuation rates in clinical trials and observational studies to examine longterm effectiveness

Table 4. Therapy characteristics as univariable and multivariable predictors of time to discontinuation among 345 patients with RA who received at least one disease-modifying antirheumatic drug (DMARD) regimen.

	Univariable Hazard Ratio (95% CI)*	Multivariable Hazard Ratio (95% CI)*
DMARD therapy characteristics		
First year DMARD use	1.09 (0.93, 1.27)	
First DMARD (vs subsequent DMARD)	1.13 (0.98, 1.30)	
No. previous DMARD		
1 (vs 0)	0.86 (0.73, 1.02)	
2	0.86 (0.70, 1.05)	
3	0.87 (0.65, 1.17)	
4–10	0.98 (0.79, 1.23)	
Concomitant DMARD use	1.20 (0.98, 1.47)	
HCQ use	0.72 (0.59, 0.87)	0.77 (0.64, 0.92)
MTX use		
Without Folate	0.56 (0.43, 0.72)	0.51 (0.39, 0.67)
With Folate	0.39 (0.30, 0.49)	0.39 (0.30, 0.51)
Prior MTX failure	1.89 (1.52, 2.34)	1.96 (1.57, 2.45)
Glucocorticoid use		
Current use	1.01 (0.86, 1.18)	
Prior use	1.07 (0.93, 1.24)	
First year use	1.23 (1.04, 1.47)	

MTX: methotrexate, HCQ: hydroxychloroquine. * From a multivariable Andersen-Gill model adjusted for age, sex, calendar year, ESR, disease duration, and Charlson comorbidity index (all at DMARD initiation).

of DMARD therapy and the differences between agents[4-34]. Despite the differences in source populations and study designs, all these studies consistently demonstrate that DMARD continuation rates are extremely low, with the majority of DMARD regimens (except for MTX) being discontinued within 1–2 years. In these studies, patients continued MTX for 3–4 years, and the main reason for MTX discontinuation appeared to be adverse effects[15]. However, findings of previous studies have been inconsistent, mainly due to the difficulties associated with unraveling the independent effects of disease duration, DMARD sequences, and the type of DMARD in prevalence cohorts[4-7,13]. Further, despite the pressing need to predict future DMARD response at disease onset, none of the previous studies started followup at RA incidence, making it impossible to assess the predictive value of disease and therapy characteristics during the first year of the disease[38]. We were able to address important aspects of DMARD response that were not addressed in previous studies of this kind, including disease duration, DMARD sequences, the distinction between early and late predictors of DMARD response, concomitant folate supplementation with MTX treatment, and use of glucocorticoid therapy. This was feasible because of our unique population-based data resources, as discussed below.

This is the first study to examine response to DMARD therapy in a population-based inception cohort with continuous and comprehensive followup for over a decade, starting at incidence date and continuing until death or the end of the study. Indeed, 86% and 63% of RA patients were still under observation at 5 and 10 years after incidence date, respectively. With this unique capability, we were able to distinguish first versus subsequent, and single versus multiple DMARD regimens, comorbidities, and disease and therapy characteristics, at both early and late stages of the disease. Additionally, our analytical methodology[50] allowed us to account for the fact that the same patient may discontinue more than one DMARD during the disease course.

A recent review article[38] concluded that the overall balance of published evidence suggests that disease duration and prior DMARD use were important predictors of DMARD response, but also acknowledged the difficulties in separating the independent effects of these factors. We were able to overcome this difficulty by starting followup at RA incidence and, for each DMARD, considering the number of prior DMARD regimens, disease duration, and DMARD type simultaneously. Our findings indicate that neither the disease duration nor the number of prior DMARD regimens had any statistically significant effect on the likelihood of DMARD discontinuation. Instead, certain DMARD (MTX and HCQ) were independently associated with longer treatment duration, while others were not. Therefore, our findings suggest that previous reports of decreased likelihood of discontinuation associated with the first DMARD use[5,14,29,33] and shorter disease duration[5,27,31,34] may in fact be due to pooling of data and failure to fully take use of MTX into account in the analyses.

Another significant observation in our study was the significant favorable influence of concomitant folate supplementation on MTX treatment duration. Despite its long-lasting efficacy, most MTX regimens are discontinued due to adverse effects that may be avoided by folate supplementation[52-57]. We were able to confirm that patients who received folate supplementation concomitantly with their MTX regimen were more likely to continue MTX for longer periods. This finding is consistent with the findings of clinical trials[53].

Further, high ESR, both at disease onset and during the disease course, was associated with a higher risk of DMARD discontinuation, whereas indicators of disease progression (e.g., radiographic evidence of joint destruction) were not, suggesting that high level of disease activity may be more closely associated with DMARD discontinuation.

Finally, glucocorticoids are an integral part of longterm pharmacotherapy of RA and are expected to influence both the initiation and continuation of therapy with individual DMARD. Two studies to date suggest that prior[5] or concomitant glucocorticoid use[4] are associated with increased likelihood of DMARD discontinuation. Our findings indicate that early glucocorticoid use (likely an indicator of high disease activity) may be weakly associated with a higher likelihood of discontinuation, but neither the prior nor concomitant use had any effect on the risk of discontinuation of DMARD.

Our findings should be interpreted in light of some potential limitations. This was a retrospective observational study that relied on clinical information recorded in the patients' medical records. Thus, disease or therapy characteristics not adequately recorded in the medical records may have been missed. Because our study (1955–2001) was conducted mostly prior to the introduction of biologics, we cannot draw conclusions regarding the role of biologics. Our findings may not be generalizable to non-White individuals because the Rochester population during the calendar years under investigation was > 95% White.

In summary, although the disease and the therapy-related predictors of DMARD discontinuation are unlikely to account for all the variability in response to therapy, our results suggest that patients who are likely to discontinue DMARD therapy in the long term can be predicted to a certain extent. MTX failure appears to identify a subgroup of patients who are more likely to fail other DMARD and therefore could perhaps be considered as candidates for new therapies. Folate supplementation extends MTX use substantially, and should be included with every MTX regimen. Importantly, in contrast to widespread belief, disease duration and the number of previous DMARD are unlikely to influence response to DMARD therapy, whereas disease activity (indicated by early glucocorticoid use and ESR) does. Future research should focus on pharmacogenomic techniques, which offer great promise to substantially improve DMARD response[40,41,58].

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