Therapeutic Strategies in Rheumatoid Arthritis Over a 40-Year Period

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ABSTRACT. ***Objective.*** To examine trends in therapeutic strategies and to identify the determinants of starting disease modifying antirheumatic drug (DMARD) therapy over a 40-year period in a population based inception cohort of patients with rheumatoid arthritis (RA).

Methods. A population based inception cohort was assembled from among all Rochester, Minnesota, residents aged ≥ 18 years who were first diagnosed with RA (1987 American College of Rheumatology criteria) between January 1, 1955, and January 1, 1995. All subjects were followed longitudinally through their complete medical records until death, migration from Olmsted County, or date of abstraction (January 1, 2001, to January 1, 2003). Drug exposure data were collected on all DMARD and corticosteroid regimens. Time to DMARD initiation was examined using the Kaplan-Meier method. The influence of calendar time and disease characteristics on time from incidence to first DMARD therapy and the number of DMARD regimens were analyzed using Cox regression and proportional odds models, respectively.

Results. The study population comprised 603 patients (73% female) with a mean age of 58 years and a mean followup of 15 years. At 2 years after RA onset, 26% of patients in the 1955–74 cohort, 40% in the 1975–84 cohort, and 70% in the 1985–94 cohort had received a DMARD (log-rank $p < 0.001$). Age, rheumatoid factor (RF) positivity, erythrocyte sedimentation rate, large joint swelling, rheumatoid nodules, and destructive changes on radiographs were significantly associated with time to first DMARD regimen after adjustment for calendar time and sex. Patients who were older and RF positive and who did not receive CS were more likely to have received more DMARD regimens.

Conclusion. Time to initiation of DMARD therapy has shortened markedly over the past 3–4 decades. These changes in management of early RA provide evidence for the translation of scientific evidence into clinical practice in rheumatology. Age and various disease characteristics are significantly associated with initiation and the number of DMARD regimens used. These should be considered as confounders when examining the effect of early DMARD treatment on disease progression and mortality. (J Rheumatol 2004;31:2366–73)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE MODIFYING ANTIRHEUMATIC DRUGS
INITIATION TIME TRENDS

Rheumatoid arthritis (RA) is a chronic systemic disease with progressive joint destruction, significant longterm disability, premature mortality, and higher lifetime costs[1-4]. There is no known cure for RA, and therefore current pharmacotherapeutic options aim at slowing joint destruction and disability[5]. Until the late 1980s, the treatment of RA was characterized by initial therapy with nonsteroidal antiinflammatory drugs (NSAID) to relieve pain and stiffness, lifestyle changes, and delayed use of disease modifying antirheumatic drugs (DMARD) for those who did not respond to initial therapy[6]. This sequential approach remained unchallenged until the late 1980s, when it was demonstrated that early aggressive therapy might have the potential to suppress disease activity before the irreversible joint damage occurs. After 2 decades of accumulating evidence, current management guidelines emphasize early detection and diagnosis and timely pharmacotherapy with DMARD to slow the progression of joint damage[5,7]. There are currently about 10 DMARD, and the choice of various DMARD alone or in combination as either the initial or followup therapy tends to be highly variable[8-22], mainly due to lack of strong evidence on their longterm effectiveness. Observational studies in population based cohorts may provide important insights to resolve some of these questions about longterm effectiveness that cannot be addressed in clinical trials. Our aim in this study was to examine trends in therapeutic strategies and to identify the determinants of

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initiating DMARD therapy over a 40-year period in a population based inception cohort of patients with RA.

MATERIALS AND METHODS

Epidemiological research in Rochester, Minnesota, is made possible by the fact that the city is relatively isolated from other urban centers and that 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, including visits to the emergency department, laboratory results, pathology reports, and correspondence concerning each patient, can easily be accessed. The potential of this data system for population based research has been described[23,24]. This records linkage system therefore constitutes a unique opportunity to study therapeutic trends in a defined nonreferred RA population.

Using this data resource, a population based incidence cohort of all cases of RA first diagnosed between January 1, 1955, and January 1, 1995, among Rochester, Minnesota, residents ≥ 18 years of age was assembled, as described[25,26]. All cases fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA[27]. 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 date of abstraction (January 1, 2001, to January 1, 2003).

Data on RA disease characteristics and the use of DMARD and corticosteroids were collected by 3 nurse abstractors according to a prespecified and pretested protocol. Iterative comparative studies were performed in which samples of medical records were reviewed by all nurse abstractors. Guided by the results of these studies, the protocol and data entry instruments were revised to reduce ambiguity and ensure agreement. Before commencing data analysis, an extensive series of checks for data consistency, proper sequences of dates, and an evaluation of missing or incomplete data was performed. Where necessary, medical records were reviewed again, and questions were resolved by consensus of the investigative team.

RA disease characteristics were assessed both at baseline (RA incidence) and throughout followup, and included rheumatoid factor (RF) positivity (≥ 40 IU/ml), erythrocyte sedimentation rate (ESR), tender and/or swollen joint counts, erosions, periarticular osteoporosis and/or destructive changes on radiographs, rheumatoid nodules (absent/present), and RA complications. ESR at RA incidence was defined as the highest recorded ESR during the first year after RA incidence. Sustained elevation of ESR was defined as ≥ 3 recorded ESR values at ≥ 60 mm/h over a minimum time interval of 30 days between the first and third measurements. Joint tenderness and/or swelling was 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 therapy. When 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. 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, immunosuppressants, and alkylating agents. Each DMARD regimen was defined as the total uninterrupted treatment time using a particular DMARD lasting ≥ 30 days. Overlapping periods of regimens lasting ≥ 30 days were defined as combination therapy. For all corticosteroid courses, data were collected on drug name, route of administration, starting and stopping dates, duration of therapy, and dosages.

Baseline characteristics of the study population and changes in use of DMARD over time were summarized using descriptive statistics. Time to start of DMARD by decades of RA incidence was estimated using the Kaplan-Meier product-limit life table method and compared using the log-rank test[28,29]. Cox regression models were used to estimate the influence of calendar time and disease characteristics on DMARD initiation[30]. Disease characteristics included those assessed at baseline as well as those assessed throughout followup. Factors assessed throughout followup were modeled as time-dependent covariates, in that an individual without one of the characteristics at RA incidence could develop it during followup. For the analysis of the number of DMARD regimens, patients were classified as having received none, one, 2, or ≥ 3 DMARD, and demographic and clinical predictors of change in DMARD therapy were examined using proportional odds models. All 2-way interactions among significant main effects were examined.

RESULTS

The study population for this analysis consisted of 603 incident cases of RA with a mean age of 58 years and 73.1% were female. Table 1 shows the characteristics of the study population at RA incidence and during the 9045 person-years of followup (mean 15 yrs). The prevalence of RA in this population was 1.08%. Over this followup period, 345 patients (57%) received a total of 753 DMARD regimens, with the majority of these patients (58%) receiving more than one regimen. In addition, 332 patients (55%) received one or more corticosteroid regimens.

Overall, HCQ, MTX, and gold were the most frequently prescribed DMARD in this cohort, with only very limited use of the newer agents (Table 2). Similarly, the most frequently used DMARD within the first year of RA were HCQ and gold. This pattern was not surprising, as 76% of the patients in this cohort were diagnosed prior to 1985, when the standard initial treatment for RA consisted of analgesics and NSAID, and the use of DMARD was typically delayed.

Utilization trends over time. For the decade 1955 to 1964, 80% of the newly initiated regimens were HCQ, compared to only about 20% in more recent years (Figure 1). Efficacy of MTX in RA was confirmed in the mid-1980s[31,32], and by the early 1990s 40% of regimens involved MTX. Almost 50% of the regimens between 1965 and 1985 were gold compounds, with a sharp decline in use in the late 1980s, following reports indicating that they may not be efficacious[33]. Other DMARD such as SSZ, AZA, and D-pen were introduced in the 1960s and 1970s, but their use never exceeded 15%, except for D-pen briefly reaching 27% in the 1970s. Use of biologics increased dramatically following their introduction in 1998.

Trends and predictors of DMARD initiation over time. Approximately 26% of patients diagnosed with RA between 1955 and 1974 received a DMARD by 2 years after inci-

Table 1. Characteristics of 603 Rochester residents (≥ 18 years of age) who first fulfilled 1987 ACR criteria for RA between January 1, 1955, and January 1, 1995.

Characteristics	At RA Incidence		Ever	
	Observed N*	N (%)†	Observed N*	N (%)†
Age, mean (SD), years	603	58.0 (± 15.2)		—
Females	603	441 (73.1)		—
Length of followup, mean (SD), years			603	15.0 (± 9.9)
RA disease characteristics				
Rheumatoid factor (RF) titer ≥ 1:40	514	302 (58.8)	574	393 (68.5)
ESR	576	46.7 (± 30.1)§	573	179 (31.2)§
Joint swelling				
Small joints	571	542 (94.9)	603	591 (98.0)
Large joints	558	233 (41.8)	603	506 (83.9)
Radiographic changes				
Destructive changes	453	93 (20.5)	535	243 (45.4)
Erosions	453	34 (7.5)	535	94 (17.6)
Periarticular osteoporosis	453	24 (5.3)	535	57 (10.6)
Rheumatoid nodules	603	35 (5.8)	603	197 (32.7)
RA complications¶	603	0 (0.0)	603	151 (25.0)
RA vasculitis	603	0 (0.0)	603	21 (3.5)
RA lung disease	603	0 (0.0)	603	24 (4.0)

ACR: American College of Rheumatology; SD: standard deviation; ESR: erythrocyte sedimentation rate; DMARD: disease modifying antirheumatic drugs. * Observed refers to the number of patients in whom the variable was measured. † No. (%) unless noted. § Value at RA incidence refers to the mean (± SD) of highest recorded ESR value in 1st year after RA incidence. Value in ever column refers to the no. (%) of patients with ≥ 3 recorded ESR values at ≥ 60 mm/h. ¶ Includes complications such as rheumatoid lung disease, vasculitis, Felty's syndrome, Sjögren's syndrome, rheumatoid myocarditis.

Table 2. Utilization of individual DMARD (for at least ≥ 30 days) among 603 Rochester, MN residents (≥ 18 years of age) who first fulfilled 1987 ACR criteria for rheumatoid arthritis (RA) between January 1, 1955, and January 1, 1995.

Medication Use (≥ 30 days)	First Year N (%)	Overall N (%)
Hydroxychloroquine	119 (19.7)	228 (37.8)
Methotrexate	23 (3.8)	142 (23.6)
PO/IM gold	87 (14.4)	181 (30.0)
Sulfasalazine	11 (1.8)	47 (7.8)
D-penicillamine	8 (1.3)	53 (8.8)
Azathioprine	3 (0.5)	31 (5.1)
Leflunomide, etanercept, infliximab	0 (0.0)	33 (5.5)
Other*	1 (0.2)	10 (1.7)
Corticosteroids	148 (24.5)	332 (55.1)
DMARD	213 (35.3)	345 (57.2)
1 regimen	174 (81.7)	145 (42.0)
2 regimens	37 (17.4)	99 (28.7)
≥ 3 regimens	2 (0.9)	101 (29.3)

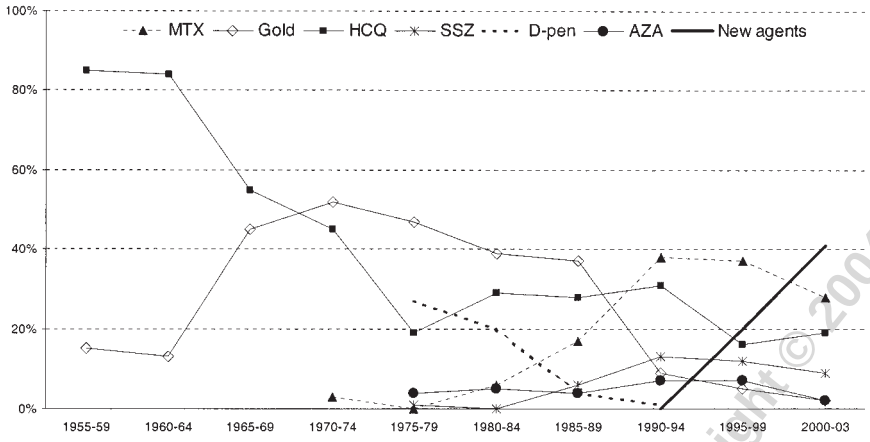
ACR: American College of Rheumatology; DMARD: disease modifying antirheumatic drugs. * Cyclosporine, cyclophosphamide.

dence, whereas almost 70% of patients in the 1985–94 cohort received a DMARD within 2 years of RA incidence date (Figure 2). These curves (Figure 2) illustrate that the main difference in DMARD use across decades was observed during the 2 years or so immediately after the diagnosis of RA.

Univariable and multivariable Cox regression models were used to assess various RA disease characteristics as predictors of initiation of DMARD (Table 3). In the multivariable model, there was a statistically significant calendar-year effect, with those diagnosed in the most recent decade (1985–94) being 7 times more likely to receive DMARD compared to those diagnosed in the earliest decade (1955–64) ($p < 0.001$). Younger patients were significantly more likely to receive DMARD early (HR per 10-year decrease in age 1.37, 95% CI 1.26, 1.46). Also, patients with more severe disease, as assessed by RF positivity (HR 1.66, 95% CI 1.20, 2.30), high ESR values (HR 1.50, 95% CI 1.01, 2.23), swelling of large joints (HR 2.50, 95% CI 1.83, 3.41), destructive changes on radiographs (HR 2.17, 95% CI 1.57, 3.01), and presence of nodules (HR 1.97, 95% CI 1.37, 2.82) were more likely to receive their first DMARD regimen compared to those who did not have these disease characteristics.

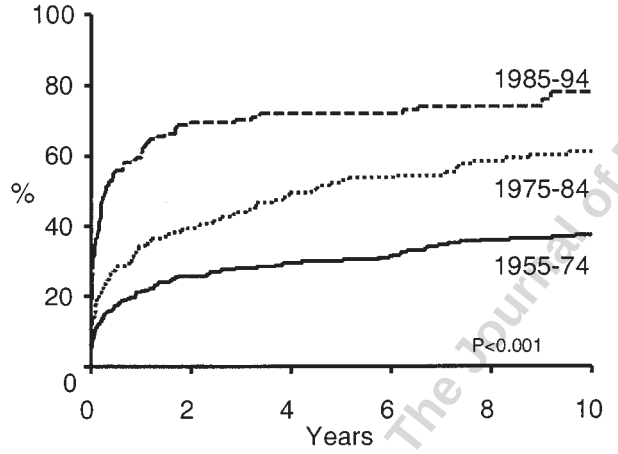
Number of DMARD regimens and predictors. Among the 345 DMARD treated patients, HCQ was the first drug in 179 (52%) patients, followed by gold in 117 (34%) patients (Figure 3). Only 24 (7%) patients received MTX as the first DMARD regimen, whereas 118 (34%) patients received MTX following another DMARD, mostly HCQ or gold. Further, very few of the MTX treated patients received another DMARD subsequently. Therefore, the most common DMARD sequences in this cohort were HCQ → gold, HCQ → MTX, gold → HCQ, and gold → MTX, respectively.

There was an increase over time in the percentage of patients undergoing combination therapy involving HCQ and MTX. Between 1975 and 1984, 23.7% of the HCQ



	1955-59	1960-64	1965-69	1970-74	1975-79	1980-84	1985-89	1990-94	1995-99	2000-03
# patients under observation	62	147	199	251	289	325	341	353	278	208
# regimens initiated	26	38	29	58	91	129	179	189	134	58

Figure 1. Changes in use of DMARD over time among 603 Rochester residents (age ≥ 18 yrs) who first fulfilled criteria for RA between January 1, 1955, and January 1, 1995.



1985-94	145	39	32	27	17	11
1975-84	157	94	74	63	50	40
1955-74	285	199	181	164	142	130

Figure 2. Time to first DMARD regimen by decades of RA incidence date.

users and 33.3% of MTX users received combination therapy, whereas after 1995, 43.7% and 41.4% of HCQ and MTX users, respectively, received combination therapy. Similarly, until 1985, only 14.4% of the DMARD regimens involved concomitant corticosteroid use, whereas thereafter it increased steadily, reaching 31.4% in late 1990s. In other words, 46.2% of patients in the 1955–74 cohort, 54.0% in the 1975–84 cohort, and 73.6% in the 1985–94 cohort had received corticosteroid at any time during the disease course.

Proportional odds models were used to assess various RA disease characteristics as predictors of the number of DMARD regimens (Table 4). The odds of receiving multiple DMARD regimens were significantly higher after 1970 (OR 4.17, 95% CI 2.93, 5.94) and among RF positive patients (OR 3.57, 95% CI 2.50, 5.08). In contrast, younger age at diagnosis (OR 1.81 per 10-year decrease, 95% CI 1.61, 2.02), and prior corticosteroid use (OR 0.67, 95% CI 0.47, 0.94) were associated with reduced likelihood of receiving multiple DMARD regimens.

DISCUSSION

We report the trends and predictors of time to DMARD initiation and the number of DMARD regimens in a population based inception cohort of patients with RA over a 40-year period. Our findings show that time to DMARD initiation has shortened markedly over the past 3–4 decades and provide further evidence for the translation of scientific evidence into clinical practice in rheumatology. Age, RF seropositivity, high ESR values, presence of large joint swelling, destructive radiographic changes, and rheumatoid nodules emerged as significant predictors of DMARD initiation and the number of DMARD regimens. All these significant predictors of DMARD initiation and switches are also associated with longterm morbidity and mortality outcomes in patients with RA. Therefore they need to be considered as confounders when examining the effect of DMARD treatment on RA disease progression and mortality, in order to adjust for confounding by indication and reduce bias.

Our findings confirm and extend the findings of previous studies on DMARD therapeutic trends[8-22]. These studies collectively demonstrate that the clinical practice in pharmacotherapy of RA has changed considerably over the last decades, with early introduction of DMARD regimens, use of multiple regimens, and major changes in type of DMARD. However, most of the studies prior to ours were cross-sectional in design, and relied on surveys of rheuma-

Table 3. Univariable and multivariable predictors of time to first DMARD initiation among 603 Rochester, MN residents (≥ 18 years of age) who first fulfilled 1987 ACR criteria for rheumatoid arthritis between January 1, 1955 and January 1, 1995.

Characteristic	Univariable, Hazard Ratio (95% CI)*	Multivariable, Hazard Ratio (95% CI)*
Age at RA incidence (per 10 years decrease)	1.24 (1.15, 1.34)	1.37 (1.26, 1.46)
Sex (male)	1.01 (0.78, 1.32)	1.30 (0.96, 1.78)
Calendar year of RA incidence		
1955–64	1	1
1965–74	1.15 (0.79, 1.68)	1.26 (0.76, 2.07)
1975–84	2.19 (1.55, 3.08)	2.91 (1.80, 4.73)
1985–94	4.00 (2.81, 5.69)	7.30 (4.31, 12.39)
Rheumatoid factor titer ≥ 1:40	2.22 (1.69, 2.92)	1.66 (1.20, 2.30)
ESR (≥ 3 values ≥ 60 mm/h)	1.24 (0.89, 1.72)	1.50 (1.01, 2.23)
Joint swelling		
Small joints	1.88 (1.08, 3.28)	
Large joints	2.35 (1.81, 3.05)	2.50 (1.83, 3.41)
Radiographic changes		
Destructive changes	1.55 (1.19, 2.02)	2.17 (1.57, 3.01)
Erosions	1.19 (0.77, 1.83)	
Periarticular osteoporosis	0.81 (0.42, 1.58)	
Rheumatoid nodules	2.22 (1.64, 3.01)	1.97 (1.37, 2.82)
RA complications§	1.23 (0.80, 1.89)	
RA vasculitis	0.56 (0.08, 4.02)	
RA lung disease	2.82 (0.89, 8.90)	
Prior corticosteroid use	1.57 (1.19, 2.08)	

ACR: American College of Rheumatology; ESR: erythrocyte sedimentation rate; DMARD: disease modifying antirheumatic drugs. * From Cox regression models with time-dependent covariates.

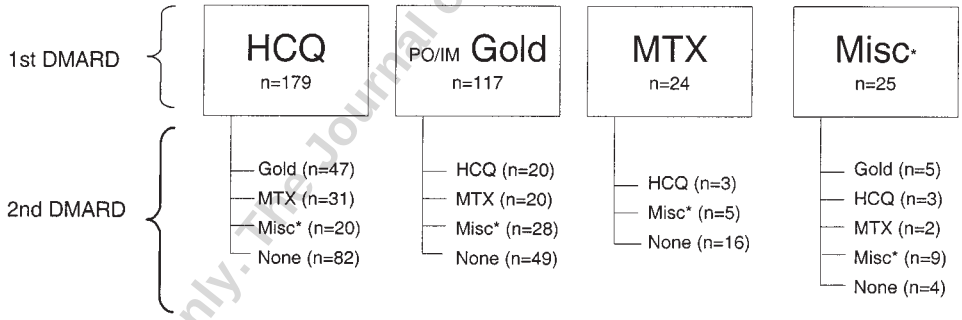


Figure 3. DMARD sequences among 345 patients who received at least one DMARD regimen. *Includes sulfasalazine, D-penicillamine, azathioprine, leflunomide, etanercept, and infliximab.

tologists. Ours is the first population based study reporting trends and determinants of DMARD therapy over almost half a century. There were only 4 studies to date that examined trends over time[19-22]. Although the periods covered in these 4 studies were much shorter than ours, the findings were very similar. Galindo-Rodriguez, *et al* reported on trends in DMARD initiation in a referral cohort of patients ascertained in Edmonton, Canada, over a 10-year period between 1985 and 1995[19]. This period corresponds to the last decade of observation in our cohort, and their observations are very similar to ours: more than 70% of patients diagnosed with RA during this time period received an initial DMARD prescription within 1.5–2 years of disease onset. Aletaha, *et al* examined prescription patterns of individual DMARD over a 28-year period[20]. Although the study was conducted in Austria, the patterns with individual DMARD are similar to ours: sharp decline in use of oral gold in the late 1980s, and almost 40% of regimens involving MTX starting early in the 1990s.

Our findings have several implications. First, utilization studies such as ours can be particularly valuable while interpreting morbidity and mortality trends in RA. Clearly, changes in DMARD therapeutic patterns over time led to considerable improvements in RA associated morbidity[34]. Yet it is still unclear whether these improvements in morbidity would also translate into improved mortality in these

Table 4. Univariable and multivariable predictors of the number of DMARD regimens among 603 Rochester, MN residents (≥ 18 years of age) who first fulfilled 1987 ACR criteria for rheumatoid arthritis between January 1, 1955 and January 1, 1995.

Characteristic†	Univariable, Odds Ratio (95% CI)*	Multivariable, Odds Ratio (95% CI)*
RA incidence date after 1970	3.46 (2.50, 4.79)	4.17 (2.93, 5.94)
Age at RA incidence (per 10 years decrease)	1.73 (1.55, 1.92)	1.81 (1.61, 2.02)
Sex (male)	1.09 (0.79, 1.52)	
Rheumatoid factor titer ≥ 1:40	3.73 (2.68, 5.20)	3.57 (2.50, 5.08)
ESR (per 10 mm/h increase)	0.91 (0.86, 0.96)	
Joint swelling		
Small joints	1.78 (0.96, 3.33)	
Large joints	0.95 (0.71, 1.29)	
Radiographic changes		
Destructive changes	0.61 (0.40, 0.93)	
Erosions	0.78 (0.41, 1.49)	
Periarticular osteoporosis	0.96 (0.45, 2.04)	
Rheumatoid nodules	1.08 (0.58, 2.01)	
Prior corticosteroid use	0.64 (0.46, 0.88)	0.67 (0.47, 0.94)

ACR: American College of Rheumatology; ESR: erythrocyte sedimentation rate; DMARD: disease modifying antirheumatic drugs. * From proportional odds models where all patients were classified as having received none, 1, 2, ≥ 3 DMARD. † Only baseline (at RA incidence) status of these characteristics were considered in prediction of the number of DMARD regimens.

patients[35-41]. Hence there is considerable interest in identifying the role of DMARD therapy on longterm outcomes. Drug utilization trends combined with studies on morbidity and mortality trends can provide ecological evidence on the possible beneficial role of DMARD therapy.

Second, although randomized trials are regarded as the gold standard in assessment of beneficial therapeutic effects of drugs, they may not be feasible under certain circumstances, such as identifying delayed effects[42]. So far, the efficacy of the various DMARD and some combinations has been assessed in clinical trials that, for a life-long disease like RA, are limited in duration, size, and representativeness of the target population. Randomized trials typically run for no longer than a year and efficacy can be assessed using only intermediate endpoints. Only 20% of RA patients in the community would be eligible for inclusion into clinical trials due to strict inclusion and exclusion criteria[43]. Limitations of clinical trials also result in inability to assess the role of disease severity, dose adjustments, comedications, combinations, and sequences, which all contribute to reduced effectiveness in the community[44]. Therefore, while clinical trials demonstrate efficacy of a particular therapeutic regimen over a short time period, they provide little information on the longterm effectiveness of commonly used therapeutic regimens (i.e., DMARD combinations, sequences) in the community. Extensive followup of population based cohorts of RA patients is an ideal data source to evaluate longterm effectiveness of various therapeutic regimens. A few recent observational studies have already attempted to address some of these real-life drug effectiveness questions[39,41,45-48]. Clearly, the pharmacoepidemiology of RA is complex. Our findings elucidate some of these complexities by summarizing the multiple dimensions of DMARD therapy, including time to initiation, type of DMARD, and combinations and sequences. These data form the foundation of future research evaluating the impact of DMARD therapeutic strategies on longterm outcomes.

Finally, the need for real-life data is probably more pressing for pharmacoeconomic assessments[49-51]. It is almost impossible to predict how favorable intermediate endpoints that are assessed in clinical trials would translate into longterm effectiveness. Further, although trials to date examined various combination regimens and management strategies, there are no trials on therapeutic sequences and strategies that are common to everyday clinical practice and cumulatively reflect the treatment experience of patients with RA. Our findings clearly indicate that patterns of DMARD therapy vary considerably in terms of time to initiation, choice of DMARD, combinations, and sequences. The longterm effectiveness and cost-effectiveness of DMARD therapy probably result from this cumulative treatment experience over years, rather than a single DMARD course. Hence the real challenges in management of RA can only be addressed if evidence from randomized clinical trials is supplemented by observational studies.

Despite all these important advantages of observational studies to examine longterm effectiveness of DMARD therapeutic strategies, they have been underutilized to date. Treatment assignment in observational studies is not randomized and the indication for treatment is commonly related to the risk of future events. This results in incomparability of prognosis between treated and untreated patients. This

phenomenon is usually referred to as confounding by indication or channeling bias and needs to be taken into account in the design, analysis, and interpretation of findings from observational studies[52-54]. Typical examples of confounders in RA are disease characteristics[55,56]. As we have shown, RF seropositivity, ESR values, large joint swelling, destructive changes, and rheumatoid nodules are all significantly associated with time to DMARD initiation, and yet all of these disease characteristics also significantly associated with overall and cardiovascular mortality[26,57,58]. Therefore any beneficial effects of DMARD therapy would be superimposed on the higher risk these patients already face. Our study provides us a unique opportunity to assess the effectiveness of various aspects of DMARD therapy on longterm outcomes, while accounting for the confounding effect of these disease characteristics.

The strengths of our study include the population based design, inclusion of a large community based RA cohort assembled over almost half a century since 1955, extensive and complete followup data on patterns of DMARD therapy and disease characteristics, and the ability to examine trends over a very long time period. Most previous studies of DMARD treatment trends were either cross-sectional or extended over much shorter time periods, and none included population based cohorts. Moreover, these previous studies were mainly based on surveys among patients or rheumatologists. We were able to ascertain the DMARD pharmacotherapy based on the complete medical records of these patients over almost the entire course of the disease.

Nevertheless, it is important to acknowledge some limitations. Our findings may not be generalizable to non-white individuals because the Rochester population during the calendar years under investigation was > 95% white. With the exception of a higher proportion of the working population employed in the healthcare industry, and correspondingly higher education levels, the local population is socioeconomically similar to American whites[24]. On the other hand, there is no assurance that local patterns of clinical practice resemble those elsewhere. This was a retrospective observational study that relied on the clinical information recorded in the patients' medical records. RA disease characteristics and DMARD therapies that were not adequately recorded in the medical records would have been missed. We were unable to ascertain the use of over-the-counter NSAID in our cohort. As a result of the years covered in this study, we have limited data on trends and predictors of use of biologics, which were introduced after 1998. Further, various healthcare characteristics could affect the likelihood of DMARD prescriptions (e.g., frequency of visits, continuity of care, rheumatologist involvement) and we did not take these into account in this analysis. Information on morbidity (e.g., quality of life, disability) was not collected in this study. Our study was not designed to address whether early DMARD use was associated with disease outcomes and mortality in these patients. This is the subject of continuing analyses.

In summary, our findings demonstrate that time to initiation of DMARD treatment has shortened markedly over the past 3 to 4 decades. Age and various disease characteristics are significantly associated with initiation of and the number of DMARD regimens. These factors need to be taken into account to adjust for disease severity and reduce bias when examining the effect of early DMARD treatment on RA disease progression and mortality.

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