# Retention rates of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis

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## ABSTRACT

**Introduction: Disease-modifying anti-rheumatic drugs (DMARDs) currently form the mainstay of treatment of rheumatoid arthritis (RA). We aimed to evaluate the retention rates of "therapeutic segments" of DMARDs in patients with RA.**

**Methods: This was a cross-sectional study of RA patients with at least one year of follow-up. A therapeutic segment is said to begin when one DMARD combination is instituted and it ends with a subsequent change. The disability index for each patient was calculated using a modified health assessment questionnaire. Retention rates were calculated using the Kaplan Meier survival analysis.**

**Results: 375 DMARD courses in 102 patients were analysed. 99 courses were being continued at the time of the study and hence were censored for the purposes of analysis. The respective median (interquartile range [IQR]) retention period for segments containing methotrexate (MTX), sulfasalazine, hydroxychloroquine and leflunomide was 28 (15–45), 12 (3–20), 18 (9–24), 15 (4–32) months. The log-rank statistical test indicated that MTX was retained longer singly (median [IQR] 43 [32–70] months) than in combination (median [IQR] 19 [10–24] months) (p-value is 0.001). The commonest reason for the discontinuation of the DMARD segment was the disease "slipping out" of control (51.1 percent) followed by adverse effects (24.3 percent). Treatment termination on account of disease control was encountered in 16.3 percent of courses only. As many as 63 percent of single DMARD segments were changed because of disease "slip out" as compared to 41 percent of combination DMARD segments. Adverse effects were a more frequent cause of termination of the combination segments (32 vs. 15 percent).**

**Conclusion: MTX, used singly, had the highest retention rates among all the DMARDs used in RA patients. Disease "slip out" and adverse effects frequently required a change of the therapeutic segment.**


**Keywords: disease-modifying anti-rheumatic drugs, methotrexate, retention rate, rheumatoid arthritis, therapeutic segment**

*Singapore Med J 2009; 50(7): 686-692*

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## INTRODUCTION

The current treatment paradigm of rheumatoid arthritis (RA) entails the early use of disease-modifying agents.[1] The various disease-modifying anti-rheumatic drugs (DMARDs) available include hydroxychloroquine, methotrexate (MTX), sulfasalazine, leflunomide, azathioprine, chloroquine, cyclosporine, gold and D-penicillamine. DMARD retention rates (RR) are important for a clinician while choosing a particular agent. MTX is currently considered the anchor disease-modifying drug due to its proven clinical efficacy and low discontinuation rates demonstrated in several long-term observational studies.[2-11] Aletaha et al demonstrated better RR for MTX (mean and standard deviation [SD] 28 ± 1 months) than for leflunomide (mean and SD 20 ± 1 months) or sulfasalazine (mean and SD 23 ± 1 months).[12] The adverse effects are the most important reason for termination of DMARDs, followed by loss of efficacy after a prolonged treatment.[13] Besides RR, there are several determinants that guide the choice of DMARDs in individual patients. These include intent to treat early, disease activity, patients' ability to afford certain medications, reasons of discontinuation of prior therapies and rheumatologist preference for certain DMARDs. Almost all the available studies addressing this issue have emanated from the West with very little information from Asian countries.[12-15] It is not known whether RR in Asian countries are similar to those reported elsewhere. In view of the paucity of information, we planned a study to estimate the RR of DMARDs in Asian Indian patients with RA and to study the factors affecting them. We studied the differences between the RR of the therapeutic segments of individual DMARDs

**Table I. Baseline patient characteristics.**

| Characteristics | No. (%) of patients |
|---|---|
| Total no. of patients | 102 (100) |
| Females | 93 (91.2) |
| Mean (SD) age (years) | 48.6 (12.0) |
| Level of education | |
| Professional degree/postgraduate | 7 (6.9) |
| Graduate | 32 (31.4) |
| Intermediate (class XI and XII) | 10 (9.8) |
| High school completion (matriculation) | 19 (18.6) |
| Primary school or literate | 21 (20.6) |
| Illiterate | 13 (12.7) |
| Occupation | |
| Housewife | 73 (71.6) |
| Unskilled worker | 2 (2) |
| Semi-skilled worker | 0 |
| Clerk, shop-owner, farm-owner | 2 (2) |
| Semi-professional | 10 (9.8) |
| Professional | 15 (14.7) |
| Socioeconomic status | |
| Upper lower | 29 (28.4) |
| Lower middle | 27 (26.5) |
| Upper middle | 46 (45.1) |

**Table II. Baseline disease characteristics.**

| Characteristics | Value |
|---|---|
| Total no. of patients | 102 (100) |
| Seropositive, no (%) | 67 (65.7) |
| Mean (SD) age (years) | 48.6 (12) |
| Mean (SD) duration of disease (years) | 11.7 (6.8) |
| Mean (SD) follow-up duration at the clinic (months) | 100.5 (69.4) |
| Median follow-up duration at the clinic (months) | 84 |
| Deformities present, no. (%) | 62 (60.8) |
| Mean (SD) disability index | 0.66 (0.51) |
| Median disability index | 0.58 |
| Functional status (%) | |
| Class 1 | 32 (31.4) |
| Class 2 | 58 (56.9) |
| Class 3 | 12 (11.8) |

used singly and in combination and also the reasons for discontinuation of individual DMARDs.

## METHODS

This cross-sectional study was carried out at the rheumatology clinic of a tertiary care hospital in north India after obtaining approval from the institutional review board. A pre-designed questionnaire, which included demographical details of the patients along with details of DMARD courses utilised during the entire course of treatment, was administered by the investigators (SA and TZ) to patients after informed consent was obtained. The study group included adult patients (> 16 years) with RA satisfying the American College of Rheumatology criteria for RA.[16] Only patients with a follow-up at the clinic for at least one year were included in the study. RA patients with other rheumatic diseases like lupus and scleroderma were excluded.

The socioeconomic status of the patient was evaluated using the modified Kuppuswamy's socioeconomic status scale,[17] and the functional status of the patient at the time of the interview was recorded using the Steinbrocker criteria.[18] A modified health assessment questionnaire, which includes activities specific to the Indian lifestyle like squatting, was used to calculate the disability index (range 0–3) of the patient at the time of the interview.[19]

The data on DMARDs were recorded using the history elicited from the patient, the medical records maintained at the hospital and the patients' personal medical records. The study centre maintains medical records of patients enrolled in the rheumatology clinic. These records hold details of DMARDs being used at each visit. Typically, patients are followed up at intervals of three months. Patients were prescribed DMARDs according to the discretion of the treating rheumatologist. No protocol was formulated specifically for this study. The concept of "therapeutic segment" was utilised to record the usage of DMARDs by the patients and subsequently to analyse the collected data. A therapeutic segment begins when one treatment is instituted and ends when a subsequent change is made.[20] A segment may thus consist of a single drug therapy or a combination drug therapy. A therapeutic segment is a definite clinical reality. The duration of a segment is a direct function of effectiveness of a drug and greater effectiveness implies that the drug is likely to be retained longer.[20] The details of DMARD segments that were recorded included the time at the beginning of the DMARD segment, duration of its use and reasons for termination of the DMARD course. Changes in drug dosages were ignored for the sake of simplicity of data collection and subsequent analysis. Short breaks in the DMARD treatment (usually four weeks or less) were counted as time taking the drug. Reinstitution of a DMARD segment after a break of more than three months was counted as an entirely new segment.

The reasons for termination of treatment were classified as adverse effects, disease "slip out", disease "in control" or miscellaneous. Adverse effects comprised any side effect that required discontinuation of a drug segment. Asymptomatic elevation of serum transaminases leading to discontinuation or alteration of DMARD segments was treated as an adverse effect. Disease "slip out" referred to the disease becoming active despite the ongoing DMARD regimen, hence entailing a change of the drug regimen. Disease "in control" referred to

**Table III. Distribution of DMARD segments and median retention periods in months.**

| DMARDs | Single | | | Combination | | | Single or combination | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of segments | No. of individuals | Median (IQR) RR (months) | No. of segments | No. of individuals | Median (IQR) RR (months) | No. of segments | No. of individuals | Median (IQR) RR (months) |
| Methotrexate | 102 | 37 | 43 (32–70) | 170 | 45 | 19 (10–24) | 272 | 66 | 28 (15–45) |
| Sulfasalazine | 27 | 14 | 11 (5–15) | 78 | 19 | 14 (3–24) | 105 | 30 | 12 (3–20) |
| Hydroxychloroquine | 10 | 5 | 9 (3–24) | 56 | 27 | 18 (9–24) | 66 | 32 | 18 (9–24) |
| Chloroquine | 8 | 1 | 4 (3–50) | 43 | 5 | 22 (9–23) | 51 | 6 | 9 (9–23) |
| Leflunomide | 11 | 7 | 8 (3–15) | 52 | 17 | 10 (7–35) | 63 | 23 | 15 (4–32) |
| Gold | 6 | 1 | 32 (32–32) | 33 | 4 | 22 (8–23) | 39 | 4 | 22 (8–23) |
| D-penicillamine | 7 | 1 | 3 (3–3) | 13 | 2 | 9 (9–9) | 20 | 3 | 9 (3–9) |
| Azathioprine | 2 | 1 | 23 (23–23) | 12 | 1 | 23 (23–23) | 14 | 2 | 23 (23–23) |
| Total | 173 | 63 | 24 (7–52) | 202 | 55 | 19 (9–24) | 375 | 94 | 22 (8–42) |

quiescent disease according to the clinical judgment of the treating physician, hence leading to termination or de-escalation of the current DMARD regimen. Miscellaneous causes included cost concerns, patient preference for complementary medicine therapy over the DMARD therapy, lack of belief, pregnancy or surgical procedures.

Statistical analysis was carried out using Stata version 10.0 (Statacorp, College Station, TX, USA). The RR for the various drug segments were estimated using the Kaplan-Meier survival analysis. The segments being continued at the time of collection of the data were treated as censored observations during the analysis. Drug discontinuation was used as an end point in the analysis. Differences between drug survival periods were analysed using the log-rank method, and median survival (in months) was determined using the Kaplan-Meier analysis. All continuous variables were summarised as mean with SD or median with interquartile range (IQR) and categorical variables as proportions. Comparisons among groups for continuous variables were made using the *t*-test. Categorical variables were analysed using the non-parametric chi-square test. Statistical significance was assumed for values of $p < 0.05$.

## RESULTS

A total of 102 patients with RA were included in the study. The baseline demographics and disease characteristics of these patients are shown in Tables I and II, respectively. A total of 375 DMARD segments were reported in these patients (average of 3.7 DMARD segments per patient). Of these, 99 DMARD segments were being continued at the time of data collection and hence were censored. The distribution of the therapeutic segments (n = 375) is shown in Table III. Of these, 173 discontinued segments consisted of a single DMARD agent and the remaining

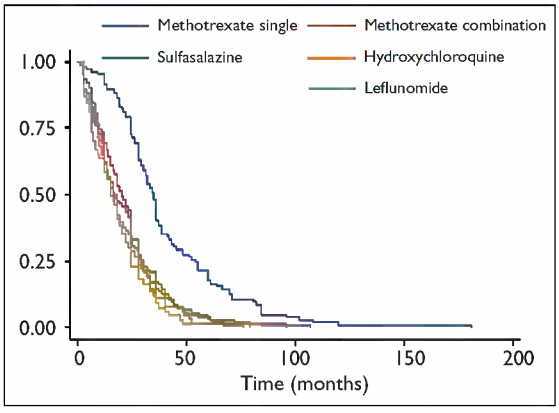


**Fig. 1** Kaplan-Meier survival curves for the commonly-encountered DMARDs.

202 comprised DMARDs in combination. MTX was the most commonly-employed DMARDs at the study site. 72.5% of the total segments utilised MTX either singly or in combination with other DMARDs. Sulfasalazine was the second most commonly-utilised drug with 28% of the segments using sulfasalazine. This was followed by hydroxychloroquine (17.6%), leflunomide (16.8%), chloroquine (13.6%), intramuscular gold (10.4%), D-penicillamine (5.3%) and azathioprine (3.7%), respectively.

The median RRs for the various DMARDs are shown in Table III. The Kaplan-Meier survival curves for MTX singly and in combination with sulfasalazine, hydroxychloroquine and leflunomide are demonstrated in Fig. 1. Among the various DMARD segments, MTX-containing segments were seen to have the highest RR (median [IQR] retention period 28 [15–45] months). Among the single DMARD segments, MTX again had the highest median (IQR) retention period of 43 (32–70) months. In our study, segments containing leflunomide were found to have relatively low retention period

**Table IV. Distribution of various DMARD segments and their median (IQR) retention in months according to the rank-order of introduction of DMARD segments.**

| DMARDs | First segment | | | Subsequent segments | | | p-value |
|---|---|---|---|---|---|---|---|
| | No. of segments | No. of individuals | Median (IQR) RR (months) | No. of segments | No. of individuals | Median (IQR) RR (months) | |
| Methotrexate | 79 | 38 | 43 (28–70) | 193 | 44 | 18 (10–24) | < 0.0001 |
| Sulfasalazine | 13 | 8 | 3 (2–8) | 92 | 26 | 16 (5–24) | 0.0610 |
| Hydroxychloroquine | 5 | 3 | 24 (19–37) | 61 | 29 | 16 (7–24) | 0.2669 |
| Chloroquine | 12 | 4 | 9 (6–23) | 39 | 2 | 9 (9–22) | 0.5521 |
| Leflunomide | 3 | 3 | 8 (4–16) | 60 | 20 | 5 (3–41) | 0.5991 |
| Gold | 5 | 1 | 18 (13–20) | 34 | 4 | 22 (8–47) | 0.9183 |
| D-penicillamine | 3 | 1 | 3 (2–9) | 17 | 2 | 9 (9–9) | 0.3173 |
| Azathioprine | 1 | 1 | 23 (23–23) | 13 | 1 | 22 (16–30) | 1.0000 |
| Total | 102 | 51 | 28 (9–60) | 273 | 69 | 16 (8–24) | 0.0030 |

(median [IQR] 15 [4–32]) when compared with the other DMARDs. 74% of the leflunomide segments had been introduced as second-line DMARD segments after termination of earlier DMARDS, either because of lack of efficacy or adverse effects due to earlier regimens. On the whole, the segments with a single agent were retained for a median (IQR) period of 24 (7–52) months, which was higher than 19 (9–24) months for the combination DMARD segments. However, this result failed to reach statistical significance ($p = 0.466$).

Fig.1 compares the retention period of segments containing MTX as a single agent vs. segments containing MTX in combination. Using the log-rank statistical test, the retention of "MTX only" segments (median [IQR] retention period 43 [32–70] months) is significantly higher than the retention of "MTX in combination" segments (median retention period 19 [10–24] months) ($p < 0.001$).

The retention periods of various DMARDs considered together were not influenced by age ($p = 0.266$), gender ($p = 0.176$) or socioeconomic status of the patient ($p = 0.866$). However, the educational status of the patient was observed to influence the RR in a significant manner. The mean (SD) retention period in patients who were illiterate or had a primary school education only was 25.2 (2.4) months as compared to the mean retention period of 32 (3.1) months in patients with a high school education and above ($p = 0.015$). With respect to the patients' occupations, housewives were observed to have significantly lower retention period as compared to those in other professions ($p = 0.046$).

The retention period of DMARDs was not affected by factors like presence of deformities ($p = 0.11$), seropositivity ($p = 0.396$) or the current functional status of the patient ($p = 0.358$). The patients who bore the cost of the treatment themselves had a mean (SD) retention period of 26 (8.4) months as compared to 29 (7.9) months for patients who were reimbursed the cost of treatment by insurance agencies or by their employers. However, this result failed to achieve statistical significance ($p = 0.315$). The current usage of complementary medicine did not seem to significantly influence the retention period of DMARDs (28.5 months in present or past users vs. 26.8 months in non-users; $p = 0.527$).

The distribution of various DMARD segments and their median retention periods according to the rank order of introduction of these agents are shown in Table IV. On the whole, it was evident that the median (IQR) retention period of the segments, which were the first introduced segments, was 28 (9–60) months in comparison to the significantly lower median retention period of 16 (8–24) months for segments which were introduced subsequently ($p = 0.003$ using the log-rank test). A similar result was obtained for the segments containing MTX. The first introduced MTX segments had a significantly higher retention period than the subsequently-introduced MTX segments. The results for other DMARDs failed to reach statistical significance.

There were several reasons reported for the discontinuation of DMARD usage. It was observed that the lack of efficacy (disease "slip out") was the most frequent reason for termination of DMARD segments, accounting for 51.1 % of the total discontinuations. This was followed by adverse effects and disease being maintained "in control" accounting for 24.3% and 16.3% terminations, respectively. Miscellaneous reasons for termination of DMARDs were cost concerns (1.1%), planned surgery (0.4%), planned pregnancy (2.2%), concomitant comorbidities (2.2%), preference of complementary medical therapy over modern medicine (1.1%) and non-compliance.

Table V shows the distribution of discontinued

**Table V. Distribution of DMARD segments and the median retention period in months according to reason of discontinuation.**

| Reason for discontinuation | Single DMARD | | | Combination DMARD | | | p-value | Single or combination DMARD | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of segments | No. of individuals | Median (IQR) RR (months) | No. of segments | No. of individuals | Median (IQR) RR (months) | | No. of segments | No. of individuals | Median (IQR) RR (months) |
| Adverse effects | 19 | 15 | 19 (2–35) | 48 | 25 | 8 (3–15) | 0.0138 | 67 | 40 | 9 (3–19) |
| Disease "slip out" | 80 | 46 | 3 (3–7) | 61 | 17 | 16 (9–19) | 0.2409 | 141 | 63 | 4 (3–16) |
| Disease "in control" | 16 | 11 | 47 (15–82) | 29 | 24 | 3 (3–17) | < 0.001 | 45 | 35 | 14 (3–24) |
| Miscellaneous | 12 | 7 | 5 (4–8) | 11 | 4 | 16 (16–33) | 0.0308 | 23 | 11 | 5 (4–9) |

segments according to the reason of discontinuation along with the median retention period for these groups. It was observed that disease "slip out" was a more frequent reason (63%) for termination of single DMARD segments as compared to 41% among the combination DMARD segments (p = 0.001). On the contrary, adverse effects were a significantly more frequent reason for termination of combination DMARD segments (32%) as compared to the single DMARD segments (15%) (p = 0.001). The termination of segments due to the disease being maintained "in control", however, was similar between the two groups (12.5% in single DMARD segments vs. 19.5% in combination DMARD segments (p = 0.65).

On analysis of the DMARD segments discontinued because of adverse effects, using the log-rank statistical test, we observed that the single DMARD segments were retained significantly longer than the combination DMARD segments, i.e. adverse effects leading to termination of a DMARD segment occurs considerably later in the case of single DMARD segments, in comparison to the combination DMARD segments (p = 0.048). A similar difference was observed during the analysis of segments terminated because the disease was maintained "in control". Single DMARD segments, which were eventually terminated for reasons of the disease being "in control", were retained for median (IQR) retention period of 47 (15–82) months, as compared to the significantly lower median retention period of 3 (3–17) months for combination DMARD segments (p = 0.001). On the contrary, the median (IQR) retention period of combination segments terminated because of disease "slip out" was 16 (9–19) which was significantly higher than that of single agents (3 [3–7] months) (p < 0.001).

Interestingly, it was observed that the patients currently using combination DMARD segments had higher disability indices as compared to the patients utilising single DMARD agent segments. The mean (standard error of the mean) disability index of patients using a single DMARD agent was 0.69 (0.076), in comparison to 0.63 (0.066) in patients using combination DMARD agents (p = 0.5931). In particular, the mean disability index of patients using "MTX-only" segments was 0.66 (0.097), which was lower than that of 0.62 (0.068) in patients using "MTX in combination" segments (p = 0.7475). Despite a trend towards significance, our results failed to reach statistical significance.

## DISCUSSION

The present study summarised the experience of a tertiary care rheumatology clinic in the long-term treatment with DMARDs for management of RA in a setting where the majority of the patients pay for the medications themselves. In this context, the setting is different from developed countries where insurance companies or the state usually pay for the drug costs. The decision to start or to stop DMARDs was dictated by the clinical condition of the patient and left to the discretion of the rheumatologist reflecting a "real life" situation in the clinic. In our study, MTX was found to be the most frequently-utilised DMARD with 72.5% of the DMARD segments utilising MTX either singly or in combination. This is in keeping with results from previous studies.[11,12,21] The RR for MTX was found to be similar to that shown by Aletaha and Smolen.[13] However, it is a little less in comparison to that determined by other studies.[18,21,22] Ortendahl et al estimated that the median number of months for MTX used singly was 41 months, and the median duration for the total duration of MTX treatment was 52 months. The RR was found to be the lowest for patients with the most negative initial health state.[20] Similar results were observed by De La Mata et al in Spain. They observed that median retention period (95% confidence interval) for patients using MTX was 51 (25–76.9) months.[22] These differences are likely attributable to the study conducted at a tertiary care centre that deals with patients who are suffering from aggressive RA and may be often refractory to medical treatment.

In our study, low RR has been observed for leflunomide containing segments similar to the observations of Aletaha et al.[12] This could be because most of the leflunomide

segments were introduced after treatment failure with other DMARDs, mainly MTX. Thus, the low RR of leflunomide observed in our study may be attributable to the fact that it was used in refractory patients. It is possible that the retention rate of leflunomide in MTX naïve patients may be different and cannot be commented upon in our study. Although, on the whole, no significant differences were observed between the retention periods of single DMARDs vs. combination DMARDs, yet the retention of "MTX only" segments was significantly higher than the "MTX in combination" segments. Selection bias could be the basis for this observation – combinations were employed in patients who had not responded to single agents, leading to a selection of patients with aggressive/refractory disease where lesser treatment benefits obtained may lead the patient to abandon DMARDs. A higher incidence of adverse effects may also contribute to the lower retention of MTX used in combination with other DMARDs.

Disease "slip out" indicating loss of effectiveness, and adverse effects were found to be the most important reasons for termination of DMARD courses in our study. Among the various adverse events, subjective adverse events were preponderant, especially gastrointestinal toxicity. Of note, disease "slip out" was a more frequent reason for discontinuation of single DMARD segments than combination DMARD segments. On the other hand, adverse effects were a more frequent reason for discontinuation of combination DMARD segments than single DMARD segments. In addition, the adverse effects leading to eventual termination of DMARD segments tend to occur relatively later for single agents in comparison to the combination DMARD segments. It was observed that the retention of DMARDs was higher in patients who were DMARDs naïve than in patients had been previously treated with one or more courses of DMARDs. This could possibly imply that the latter group of patients had a more aggressive disease refractory to medical management, which probably accounts for the low retention of subsequent DMARDs in these patients. In addition, education and occupation also seem to have beneficial effects on the retention of drugs. Those with a high school education and above had significantly higher RRs, probably due to a better understanding of the treatment courses and greater compliance with the treatment regimens. Housewives, on the other hand, seemed to have a lower retention of DMARDs as compared to other occupations. Prior studies in other settings have indicated poor compliance rates of housewives on medical care.[23] As emphasised by Pincus et al, the probability of drug continuation cannot be interpreted as reflecting directly on the patterns of drug efficacy, but drug discontinuation often reflects physician or patient biases, costs, marketing and insurance variables and other important considerations.[24]

The potential limitations of our study stem from the retrospective nature of the study and a relatively small sample size. Response was not defined beforehand and the decision to change DMARD therapy was left to the discretion of the individual clinician without any structured protocol, reflective of the real life situation in a multi-member clinic. Partial DMARD responses were difficult to characterise in our study. Another limitation of our study is the potential confounder role of steroids. In the absence of a structured treatment protocol, a change in steroid dosage could have impacted the clinical status, and indirectly, the retention rate of DMARDs in some patients.

In conclusion, a large proportion of the segments studied had utilised MTX either singly or in combination with other DMARDs. MTX used singly had the longest retention period among all DMARDs used. The RR for "MTX in combination" was significantly lower in comparison to "MTX used singly". This may be attributable to the higher incidence of adverse effects in patients using "MTX in combination". Among the various reasons for termination of DMARD segments, disease "slip out" was the most frequent reason, followed by adverse effects.

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