

The Methotrexate Therapeutic Response in Rheumatoid Arthritis

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ABSTRACT. Objective. Methotrexate (MTX) is used frequently as a disease modifying antirheumatic drug (DMARD) for rheumatoid arthritis (RA), and patients tend to continue taking this drug for longer periods than alternative single agents. The shape of the therapeutic response beyond one or 2 years, however, has not been fully studied. We examined the properties of the pure MTX “therapeutic segment,” that period that begins with start of MTX and terminates when MTX is discontinued or another DMARD is added, by observational study.

Methods. We studied new MTX starts for the period 1988 through 1996 for 437 patients from a parent cohort of 4253 patients. Patients were drawn from 8 Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) data centers: 2 community based populations; 2 private rheumatological practices; 2 university referral practices; and 2 university clinics for underserved minority urban populations. Health Assessment Questionnaire (HAQ) Disability Index scores (0–3) were obtained prospectively each 6 months.

Results. At MTX start, patients had relatively long average disease duration of 16.7 years, and had moderately severe disability, with an initial HAQ mean disability score of 1.48. Over the 10 year period examined in the parent cohort of 4253 patients (and thus irrespective of therapy), the prevalence of MTX use rose from 19% to 45%, while mean HAQ disability declined from 1.34 to 1.11. This correspondence is consistent with an accrual of benefits from more frequent use of MTX and other DMARD over this period. The MTX therapeutic segment revealed a distinct shape. HAQ-Disability Index values began at 1.48 at baseline and declined to a maximal improvement of 1.23 at 30 months. This long period to maximum benefit may have been partly driven by a slow titration upward to an optimal dosage. After 42 months, disability for this population began to re-progress and reached 1.39 at 84 months, still below the pretreatment baseline. Re-progression to baseline was about 8 or more years. Cumulative disability averted with MTX treatment for this population was roughly 1.30 disability-unit-years.

Conclusion. MTX treatment of RA in practice differs substantially from common perception and appears suboptimal by being too little, too late, and too long to treatment change. A modification of the “sawtooth strategy” in which the disease is “ratcheted down” by change of MTX therapy at 3 years or when re-progression has proceeded halfway to baseline, rather than waiting for return to baseline, is suggested by these data. Also suggested is the need for more rapid upward dosage titration and longer maintenance of an optimal or highest tolerated dosage. “Therapeutic segment” data provide insights into strategic approaches to management of RA since they allow estimation of population aggregate properties such as time to maximum benefit and the time to return to baseline. (J Rheumatol 2002;29:2084–91)

Key Indexing Terms:

METHOTREXATE
THERAPEUTIC SEGMENT

RHEUMATOID ARTHRITIS TREATMENT
LONGTERM TREATMENT

Increased use of disease modifying antirheumatic drugs (DMARD) in rheumatoid arthritis (RA) has been correlated with mitigation of longterm disability¹. Patients treated

consistently with DMARD based strategies early in the disease course have substantially improved functional outcomes compared to patients treated principally with nonsteroidal antiinflammatory drugs (NSAID)²⁻⁴. Newer strategic approaches involve sequential deployment of specific DMARD and DMARD combinations over a long disease course, but optimal sequences and optimal times to treatment change have not been studied.

The “sawtooth strategy”⁵ and other newer strategies employ early, aggressive, and consistent use of single DMARD drugs and DMARD combinations, setting a strategy for management of the entire disease course. Disability and other outcome variables are regularly moni-

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tored so that disease progression may be plotted serially, and a ceiling set in terms of allowable disability, which traditionally has been a return to pretreatment baseline values. Progression of disability beyond a predetermined value triggers a decision to change treatment. DMARD therapy is serially changed to a new regimen by addition, subtraction, or substitution of agents at each decision point. Evidence has been presented supporting the “sawtooth strategy”⁶, but estimation of optimal decision points has not been addressed. The default decision point⁵ has been when benefit achieved from baseline with a particular agent has been lost.

Much recent research has focused on use of patient oriented RA outcomes. A broader and more compassionate view of chronic illness mandates inclusion of patient oriented outcome indicators such as disability, pain, and quality of life⁷⁻⁹ in clinical studies and in patient care. Disability frequently has been assessed by using the Health Assessment Questionnaire Disability Index (HAQ-DI), which has become the most widely used instrument for disability assessment in RA, developed and described by Fries, *et al*⁷⁻¹⁰. Literally hundreds of studies¹¹ have shown the HAQ-DI to be a sensitive indicator of change over time and often more sensitive than other outcome variables, particularly on a longterm basis⁹⁻¹³. Comparisons of relative accuracy and sensitivity to change among 14 different outcome indicators in patients with RA over 60 weeks found the HAQ-DI to be the most sensitive of the measures examined¹⁴⁻¹⁷.

Traditionally, we study drug treatments by clinical trials over fixed periods of time, in essence creating severely right-censored data. However, when we treat patients we do not employ treatment periods of fixed length, and treatment durations frequently exceed the period studied in trials. In this context, a largely unexplored concept is the “therapeutic segment,” which begins with the start of one treatment and ends with discontinuation of treatment, addition of an alternative agent, or start of a new treatment. Study of therapeutic segments is a potentially illuminating approach to the analysis of treatment decisions and is well suited for area-under-the-curve estimation. Therapeutic segments for different agents have different expected durations; treatment with methotrexate (MTX) presently appears to have the longest duration^{18,19}.

MTX has been found to decrease functional disability^{14,18} and to favorably affect health of the patient with RA in a number of other ways. It has become the most popular DMARD and the DMARD patients continue taking longest. Significant reduction in disability has been shown at 3 months, with dramatically increased improvement at 9 months^{14,15}. Because MTX has data available for relatively longterm data periods, direct study of the entire therapeutic segment is permitted, rather than only the early part of the course, as currently limits experience with

newer agents such as leflunomide, etanercept, infliximab, and anakinra.

A recent study by our group¹⁹ showed that the expected duration of the MTX therapeutic segment was influenced by clinical variables such as disability, pain, and global assessment. Use of these indicators allowed identification of those patients likely to have more or less satisfactory experiences with MTX. According to the “sawtooth strategy,” a suggested rule has been to change therapy when the disability level, over time, has returned to or surpassed the baseline value. Other possible rules might be to change treatment at any point when another available treatment has a more favorable predicted response, or after a particular time, or when disability has begun to re-progress after initial improvement.

We studied the therapeutic response of MTX for up to 10 years in a large, prospective RA cohort, in order to (1) estimate the time required for disability levels to return to baseline after initial response, (2) determine the time to maximal improvement, (3) estimate the population-aggregate cumulative amount of disability averted, (4) examine whether responses in those with shorter periods of treatment tracked with those with longer segments, and (5) examine treatment use and effects in actual clinical practice to assess adherence or lack thereof to the current conventional wisdom.

MATERIALS AND METHODS

Patients. ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) is a multicenter chronic disease data bank system with serial data that span more than 2 decades for many subjects. Patients have been described¹⁹. All met the 1987 American College of Rheumatology (ACR) classification criteria for RA²⁰ and were enrolled consecutively. The full cohort for this study contained 4253 patients, of which 437 had new MTX starts.

Data bank centers representing 8 separate patient populations were used. Two centers (Santa Clara County, California, USA, and Saskatoon, Saskatchewan, Canada) were community based populations; 2 centers (Wichita, Kansas, and Phoenix, Arizona, USA) were private rheumatological practices; 2 centers (Stanford, California, and Montreal, Quebec, Canada) were university referral practices; and 2 centers (Cincinnati, Ohio, and Baltimore, Maryland, USA) were university clinics for underserved minority urban populations. Consecutive patients were enrolled and followed prospectively at each center using standard ARAMIS protocols with followup each 6 months. Patients were required to have completed at least one HAQ prior to starting MTX; this requirement eliminated many patients who received MTX. HAQ data obtained just prior to the MTX start served as baseline.

Each patient was allowed to contribute only his/her first MTX segment. Patients had “new MTX starts” where they were known not to have been taking MTX in the prior observation period. To qualify as a new MTX start, patients could not be taking any other DMARD when they started MTX. There were no other restrictions and patients were allowed to use NSAID and prednisone while taking MTX. The end of the therapeutic segment was computed from that point at which MTX was stopped or when another DMARD was added.

Measurements. The principal outcome measure, the HAQ, was developed by ARAMIS and the Stanford Arthritis Center to measure health status and service utilization over the long term. Patient information was assessed by HAQ every 6 months before and during the segment of treatment. Factors assessed included clinical information, demographics, diagnoses, symp-

toms, physical signs, laboratory findings, therapy employed, disability, therapies, side effects, and economic effects.

The outcome variable was the Disability Index of the HAQ. The DI assesses functional ability in 8 component categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, outside activity). Respondents were asked to rate their ability at each activity over the preceding week on the following scale: 0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; 3 = unable to perform. The DI is calculated as the sum of the highest scores in each category divided by the total number of categories answered, if 6 or more. DI scores may range from 0 to 3. No DI scores were missing for any of the 2669 observations on MTX segments in this study.

Analyses. For the data presented here, a time value of 0 represents the time at which the most recent measurement of disability was obtained prior to any usage of MTX and thus prior to any modification of disease progression by this agent. Cumulative disability scores are for each 6 month period (HAQ phase) while the patient continued taking MTX, and are summed.

Analyses of panel data employed generalized estimating equations (GEE) with an inverse link and a compound symmetric covariance structure. Although HAQ disability is bounded above (at 3.0), the canonical link of the gamma family was used because conditional distributions of HAQ disability by elapsed HAQ phase were right-skewed and the coefficient of variation appeared to be stable across elapsed HAQ phases.

Cumulative disability averted (CDA) was calculated from an ordinary least-squares fit to the raw means of Figure 2 as:

$$CDA = \int_0^{\tau} [\hat{p}_0 - (\hat{p}_0 + \hat{p}_1x + \hat{p}_2x^2 + \hat{p}_3x^3)]dx,$$

where the $\{\hat{p}_i\}_{i=0}^3$ are the estimated polynomial coefficients (\hat{p}_0 being the estimate of baseline disability) and τ is elapsed time up to which CDA is calculated.

To investigate the possibility that the MTX segment depicted in Figure 2 was affected by changes in MTX dosage over time, 2 inverse-link GEE were fit. The first regressed HAQ disability on MTX dosage, while the second regressed HAQ disability on MTX dosage plus linear, quadratic, and cubic terms for elapsed months taking MTX. This procedure permitted exploration of a dosage effect that may have been confounded with time.

RESULTS

Among the 437 patients with MTX starts, 82% were female. On average at baseline, these patients were 59 years of age, with an age at disease onset of 42 years, a disease duration of 17 years, and a high school education. Patients averaged less than one comorbid disease condition each.

Figure 1 shows the time course (January 1, 1988, through January 1, 1996) of average HAQ-DI scores for the 4253 patients and the prevalence of MTX use over a similar period. Increasing use of MTX and declining disability scores were seen, consistent with a positive DMARD effect. MTX use rose from 19% to 45% over this period. Average disability declined from about 1.32 in 1988 to 1.25 in 1996. The data of Figure 1 do not, of course, provide proof of a causal relationship between increasing use of MTX and other DMARD and lesser amounts of disability, since the disease could have been becoming milder over time or other treatment could be responsible. For example, the GEE model did find statistically significant effects of time on HAQ disability (linear term $p = 0.01$, quadratic term $p = 0.04$, cubic term $p = 0.02$), but failed to find an additional effect of MTX usage ($p > 0.2$) beyond that explained by

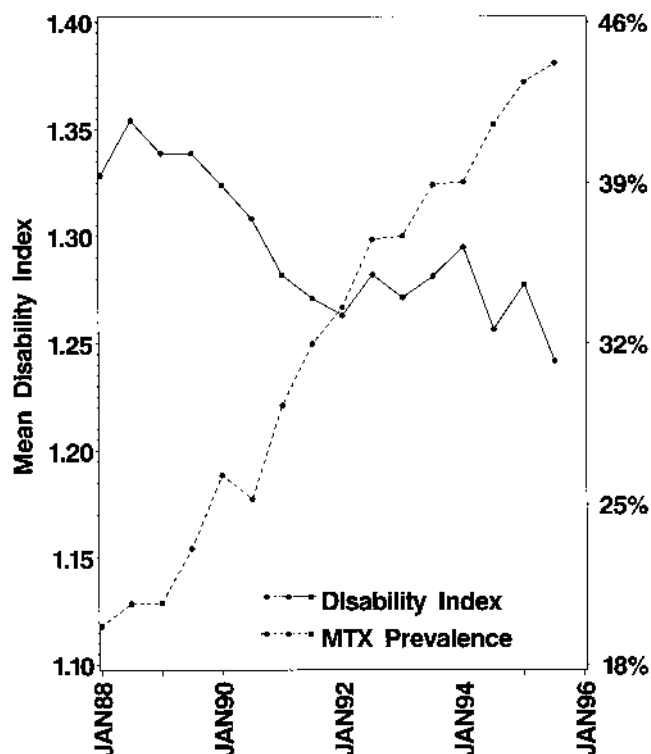


Figure 1. Mean HAQ Disability Index and prevalence of MTX use over time. Prevalence of MTX use increased steadily in the full cohort from 1988 to 1998. Concurrently, mean disability of the cohort declined steadily despite increasing disease duration.

time as a predictor. This is most likely due to the high degree of correlation between prevalence of MTX usage and time.

We plotted disability levels against time-taking-drug to directly assess the cumulative effect of MTX therapy over time and the shape of the population-aggregate therapeutic response curve. Figure 2 shows the first 84 months of the time course of mean HAQ scores for the 437 patients with new MTX starts; this represents an intention-to-treat analysis. Raw means, means adjusted for within-subject correlation, an ordinary least-squares cubic-polynomial fit to the raw means, the GEE cubic-polynomial fit, and 95% confidence bounds on the predicted means from the GEE fit are plotted in Figure 2. Across members of this population, improvement in average disability was steady in the first part of the MTX therapeutic segment. The estimated population curve plateaued from roughly 30 to 42 months, after which re-progression began to occur. Nearing 84 months, this aggregate process showed a slow rise in disability, but improvement from baseline persisted. The mean HAQ-DI was roughly 1.48 at baseline, 1.26 at 42 months, and 1.39 at 84 months, and disability was lowest (1.23) at about 30 months. Estimated cumulative disability averted to 84 months was about 1.20 disability-years; and if the curve is extrapolated to return to baseline, estimated disability averted is about 1.30 disability years. Figure 2 truncates data

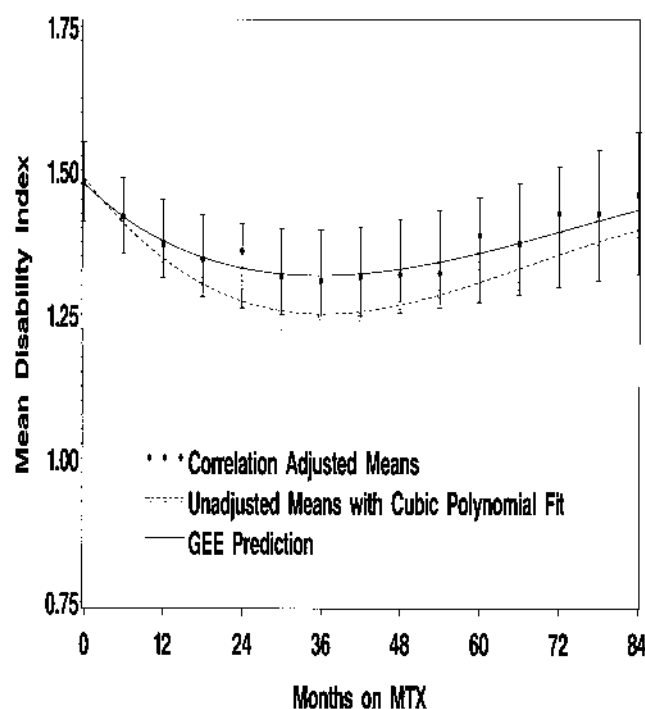


Figure 2. Prospective analysis of mean HAQ Disability Index during MTX therapeutic segment for the 437 patients with new MTX starts. Figure is truncated at 84 months. Bars show 95% confidence limits on means predicted by the GEE fit.

and regression fits at 84 months because the number continuing to take MTX beyond this point was fewer than 50. Patient characteristics for those taking MTX for more or less than 84 months are contrasted in Table 1. Patients taking MTX for more than 84 months were younger, with shorter disease duration, and with slightly less disease duration at baseline. Figure 2 also shows that effectiveness of MTX on disability is slightly less with the correlation-adjusted mean values and GEE fit, but the shape of the response does not change materially.

We were surprised by the continued improvement into the fourth year of treatment, since the literature generally supports a prompt response to MTX over weeks to a few

Table 1. Baseline demographics by duration of course.

Baseline Values	Courses \leq 84 mo, n = 409	Courses $>$ 84 mo, n = 28
	Mean (SE)	Mean (SE)
VAS global	50.1 (1.1)	48.8 (4.0)
VAS pain	1.57 (0.04)	1.40 (0.15)
HAQ disability	1.48 (0.04)	1.38 (0.15)
Years of education	12.3 (0.1)	12.3 (0.45)
Percentage female	18 (2)	21 (8)
Age, yrs	58.9 (0.7)	54.2 (2.3)
Disease duration, yrs	16.9 (0.6)	12.9 (1.6)

VAS: visual analog scale, HAQ: Health Assessment Questionnaire Disability Index score.

months. We hypothesized that the most obvious explanation for this long delay to maximal effectiveness was that due to increasing MTX dosage during MTX segment. Figure 3 displays this relationship, providing the 6 to 84 month time course of the raw mean MTX dosages. Mean dosage rises and falls over the same period during which mean HAQ-DI correspondingly falls and then rises, although the variation in dose is relatively small. GEE analysis found MTX dosage to be a significant predictor of HAQ disability when MTX was the only predictor in the model ($p < 0.001$). However, when linear, quadratic, and cubic terms for time were added to the model, we no longer found MTX dosage to be a significant predictor of HAQ disability ($p > 0.2$), because dosages were covaried with time (Figure 3). Dosage titration occurred similarly in subgroups from different data-bank centers, suggesting a generalizable pattern. For instance, during the first 84 months peak dosages were 9.91, 11.04, and 11.37 mg/week at 42, 42, and 60 months for Saskatoon, Stanford, and Wichita, respectively.

Patients continued taking MTX for various durations before cessation or addition of another DMARD. Some treatment courses ended with treatment change, while others were right-censored when the patient continued taking the drug to the last recorded visit. Right-censoring can make a drug look more or less effective, depending on whether the

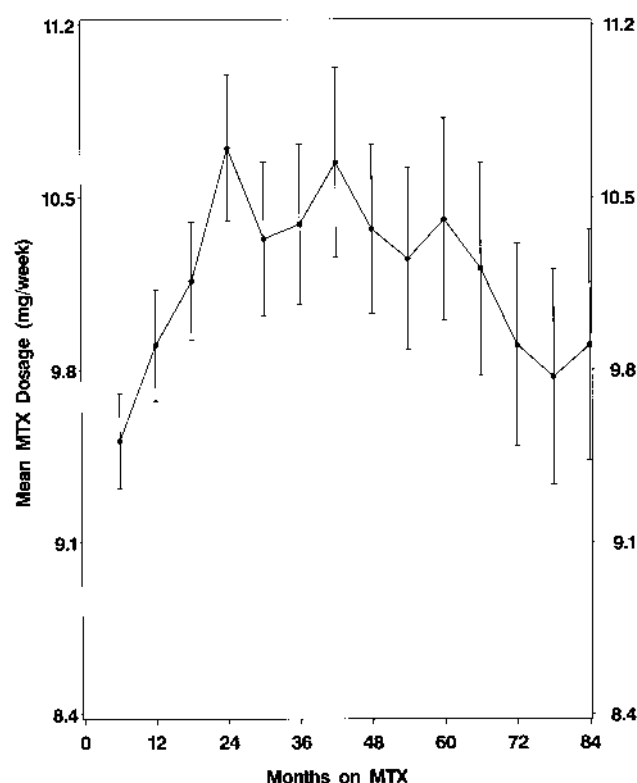


Figure 3. MTX dosage plotted on elapsed months taking MTX. Values are raw means. Bars are standard errors on raw means. Average dosage rises over the first several years and then declines.

best responders or the worst are more likely to change treatments, and is an important potential source of bias. Figure 4 confronts this bias by comparing therapeutic segments for those who made a therapeutic change against those who were right-censored. Patients changing therapy had an average disability level of 1.52 before starting MTX compared to 1.44 for those continuing the drug. This difference at baseline was not statistically significant (permutation test $p > 0.2$), nor was there a statistically significant difference in disability over the period of 0 to 60 months (the period of the curves' overlap (inverse-link GEE $p = 0.1108$). The 2 groups' curves are similar in shape and appear to yield roughly similar amounts of CDA from baseline.

Given differing lengths of therapeutic segments, we wished to see if the shape of the therapeutic response curve was related to the duration of therapeutic segment. Figure 5 gives separate time courses of raw means for all patients completing 18, 30, 42, 54, 66, and 84 months of treatment, representing an intent-to-treat analysis. The curves follow one another in part because the same patient contributes to any curve of the same length or shorter than his/her

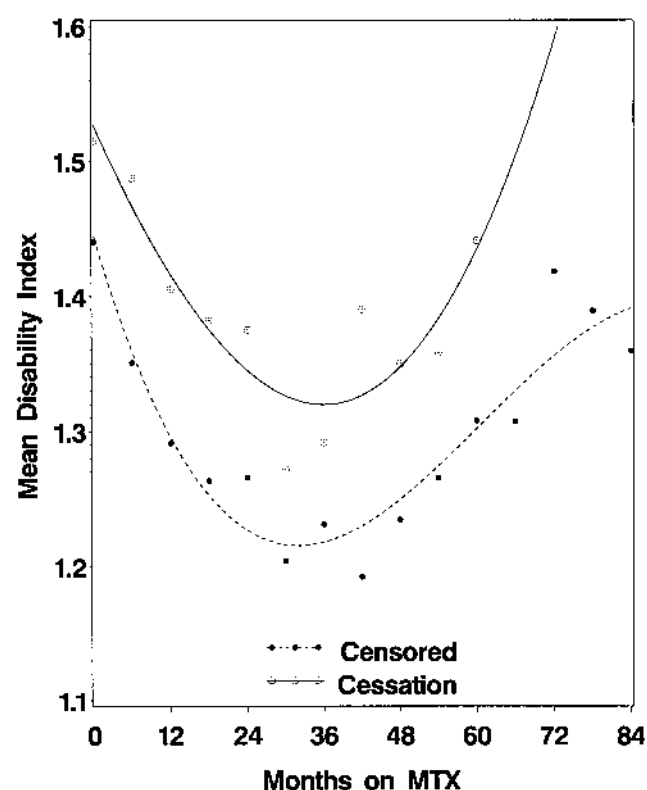


Figure 4. Differences in disability response between right-censored and MTX-cessation subgroups. ●: raw means for right-censored patients; ○: raw means for patients who left the pure MTX course during followup. Lines represent fitted cubic polynomials to each set of raw means. While curves are similar in shape, those who continued taking MTX at last observation had initially less severe disease and tended to use MTX longer than those who had discontinued treatment prior to last observation.

segment. About 6% continued MTX for over 84 months with a sustained reduction in measured disability. Another group of 69 patients stopped MTX after 30 to 48 months despite sustained depression of disability. Those that continued MTX for 54 to 84 months experienced a response not unlike that for the population aggregate (Figure 2), except that average final disability may have exceeded the average at baseline.

We also assessed mean disability index scores for all 4253 participating patients in the ARAMIS cohort against months elapsed from first HAQ (January 1988). Based on the difference in predicted average disability between 1995 and 1988 (inverse-link GEE), disability showed a slow rate increase of about 0.02 units per year. This indicates that the above calculations of disability-years averted with MTX are conservative, because those calculations assume retention at baseline as a reference. The rate of 0.02 units per year represents a recent “unnatural history” of RA in that this estimate of disability progression is lower than earlier estimates. Although lower, it is not yet satisfactory, perhaps because truly optimal treatment strategies, optimal prescription practices, perfect patient adherence, and newer available treatments are not incorporated.

DISCUSSION

This is the first study to describe details of the therapeutic response to MTX in RA. Use of the concept of the therapeutic segment reveals clinical insights not previously noted, indicates that much MTX use is suboptimal, and suggests new clinical approaches. The return-to-baseline method used likely underestimates disability averted because the baseline criterion fails to account for disease progression in the absence of MTX treatment.

We were surprised that in some cases improvement continued to accrue into the fourth year after treatment start; our initial expectation was that clinical improvement would be maximal after 6 months. The protracted response suggests that dosage titration of MTX may have been slower than desirable (Figure 3) and that some therapeutic benefit may thereby have been lost, that the effects of the drug truly accumulate over quite a long time, and/or that the exercise and activities permitted by a partial therapeutic response, and improved personal self-efficacy, extend rehabilitation improvement into the third and even fourth years of treatment¹³.

Among these explanations for protracted improvement, dosage response appears particularly likely (Figure 3). This raises new clinical issues. On average, our participating centers' physicians took 3 or more years to reach what seemed to be an optimal dosage, and these data represent the clinical decisions of 8 centers, scores of physicians, and hundreds of patients. It seems likely, therefore, that they represent a reasonable perspective on practice in the real world. This indicates that physicians take a more cautious

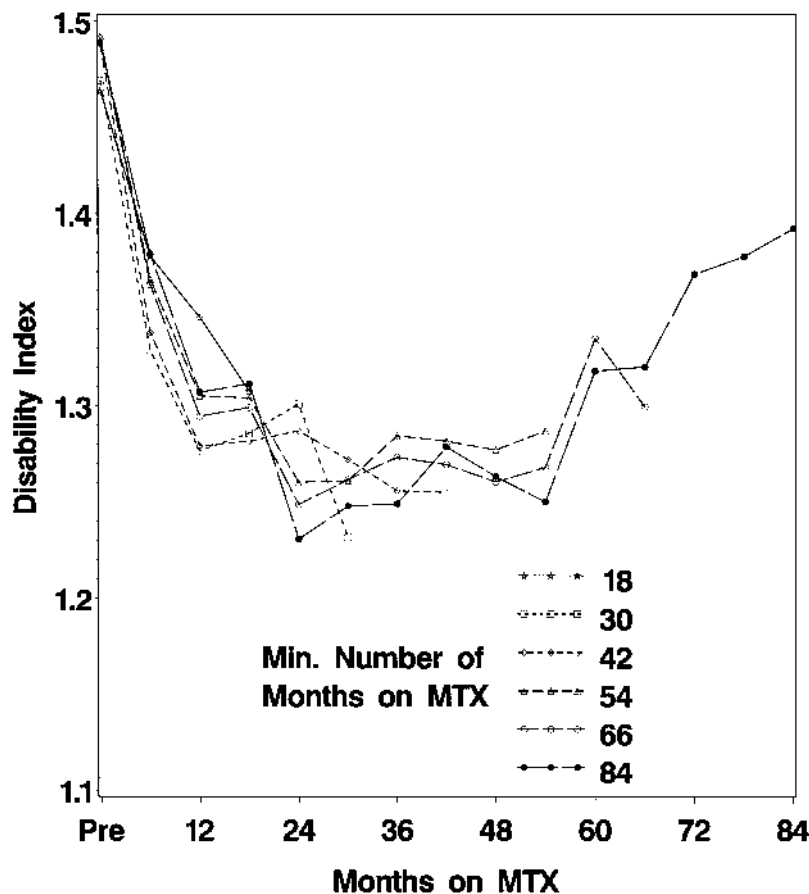


Figure 5. Mean HAQ Disability Index course during MTX segments of differing lengths: retrospective analysis of overlapping groups. A patient contributed to any curve that was at least as long as his/her full course.

approach to raising MTX dosage than we had anticipated, with multiple clinic visits required between each upward adjustment. Taken together, the disability response and MTX dosage curves suggest that cumulative disability might have been reduced considerably for this population if prescribers had consistently performed titration in the first 6 months to the point of toxicity or to some lesser predetermined maximal level for the patient.

Similarly, our clinics' physicians generally espouse the belief that aggressive DMARD treatment needs to be continued throughout the disease course. Yet those patients who continued MTX longest received only modest dosage increments over their segment and on average never did use high or relatively high dosage. Dose was actually decreased later in the segment. Dosage thus appears to have been suboptimal. Again, this is extremely cautious given current standards, perhaps reflecting older concepts of liver biopsy requirements after fixed total dosage amounts of MTX. Dosage appears to have been increased most rapidly among those patients with more abbreviated MTX segments.

We also were surprised that a relatively large proportion of patients discontinued MTX even while at or near

maximal therapeutic benefit. This observation invites more detailed study of reasons for discontinuation, such as the appearance of a new drug on the market or increasing fear of toxicity in contrast to actual manifestation of toxicity. Such factors may be influencing physician and patient behavior (perhaps to the detriment of optimal longterm outcome). Clearly, "lack of efficacy" or "toxicity" are only 2 of many reasons for medication changes in actual clinical practice.

When evaluating patients with RA, a distinction is frequently made between disease activity and damage outcomes¹⁵. The improvement found in this study in a sizable proportion of relatively late-stage patients suggests continuing inflammatory activity even in late RA, and argues for MTX treatment (or alternative DMARD treatments) even in patients with substantial damage and putatively fixed pathology. This improvement in longterm outcomes is in contrast to earlier longterm studies that were unable to detect differences in disability outcomes between those who received certain medications and those who did not^{7,21,22}. Recent studies have had more optimistic findings²³⁻²⁶.

The “sawtooth strategy”⁵ suggested that our best RA strategy is early, consistent, aggressive treatment with DMARD alone or in combination, and that treatment changes or additions should be made whenever the disability level rises above baseline for that patient, in order to prevent progression of disability. This study for the first time confirms that for some patients therapeutic segments actually look like the curve between 2 saw teeth, and that the distance between “teeth” can span several years. However, many patients may not show the classical sawtooth response, in part because they are either short term nonresponders or longterm responders.

These data also suggest that the “return-to-baseline” decision strategy may be too conservative. Physicians and patients usually change treatment before that point. It may be preferable to begin a new treatment earlier, before reprogression has occurred. Alternative decision points that might be considered include (1) elapsed time-taking-drug (e.g., 24 to 36 months for MTX, which would approximate the time of maximal response); or (2) a point at which estimated optimal benefit below baseline has been reached, about 0.23 HAQ-DI units for MTX (Figure 2); or (3) the time when the appearance of re-progression (perhaps at 48 months on average) is noted. Each of these represents a decision strategy of “ratcheting down” the disability due to RA with successive turns of treatment. The availability of a number of new and perhaps more powerful agents and combinations only enhances the feasibility of this approach; when MTX was clearly the best available treatment, it was more reasonable to stay with it for a long time. On the other hand, since disability may continue to decline for over 2 years with MTX treatment, a change made any sooner (except for toxicity) may be premature.

Effective clinical guidelines require a decision model based on empirical data about the likely future time course of events. Pre-approval drug trials are fixed in length, often lasting 6 months to 2 years. In practice, treatments must be sustained over the long term, and changes appropriate to the patient cannot reasonably be made exactly at 6 months, one year, or 2 years. Clinical trials are by definition right-censored and have defined lengths. The clinical concept of the therapeutic segment that begins with the start of one treatment and ends with the discontinuation of treatment or the addition of an alternative agent meets these needs. The concept of the therapeutic segment enables computation of clinically useful variables such as time to maximal benefit, time to return-to-baseline, and cumulative area-under-the-curve disability averted, as well as permitting differentiation of patients’ responses.

Therapeutic segments of different DMARD have different lengths. Segments for MTX currently have the longest duration¹⁸. Typical duration for the therapeutic segment of MTX was found to be 41 months¹⁹, and for the full segment on drug with or without additional therapy was

52 months. Time for return-to-baseline is longer still. More potent drugs and drug combinations are appearing, but with a foundation of relatively short term clinical experience. We can use the graphic techniques of the figures shown here to map the shape of the segment for new agents as data become available, which can permit informed development of treatment decision strategies appropriate to the evolving pharmacy of available agents.

Other problems with the literal use of expectations derived from clinical trials in the clinical setting are suggested by these data. In practice, treatment changes are made without washout periods²⁷, later in the disease course, in patients without exclusions, and in a setting influenced by patient and physician fears of future toxicity. As a result, the decisions appear substantially more conservative than would have been the case if they had been based upon clinical trial data.

The concept of the therapeutic segment can employ outcomes other than disability wherever greater breadth of information is available. For example, pain-unit-years, toxicity-unit-years, and cumulative dollar costs can be examined in terms of the therapeutic segment.

We prefer the term “therapeutic segment” to the similar term “treatment course.” The reason is that in RA and many other chronic illnesses the clinical treatment course has a past and a future, and represents a segment connecting the two. The response to treatment is in part a function of the immediately prior treatment²⁷. Decision strategies require that we consider the past and future course of the patient as well. We do not now and may never have a single 25 year remitting drug or drug combination that would render complex decision rules irrelevant. It is likely to get more complicated before it gets simpler. We need to optimize longterm cumulative outcomes with sequencing strategies that sequentially employ a number of specific treatments.

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