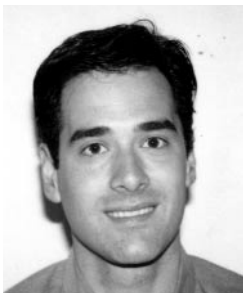
Editorial

Monitoring Methotrexate Hepatic Toxicity in Rheumatoid Arthritis: Is It Time to Update the Guidelines?



Methotrexate (MTX) is the most commonly prescribed disease modifying antirheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA)[1]. It is one of many medications not developed specifically for rheumatology but found to be useful in the treatment of RA. Rheumatologists have benefited from the experience following use of this drug by other subspecialties.

MTX was initially developed as an antimetabolite that was first used successfully in the treatment of leukemia and other malignancies[2]. This was followed by its use in organ transplantation and psoriasis[3,4]. Data from these disparate disease populations were employed in defining the monitoring algorithms in patients with RA.

In 1994, the American College of Rheumatology (ACR) published guidelines for monitoring the development of hepatic toxicity related to MTX[5]. These recommendations include measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin, collectively referred to as liver function tests (LFT), every 4–8 weeks. Evaluations of the complete blood count (CBC), platelets, and creatinine would also be performed at baseline and most rheumatologists repeat these at intervals.

The necessity and cost effectiveness of routine monitoring of all patients with RA receiving second-line agents for the development of hepatotoxicity has been questioned[6], and this led us to look at the issue of the potential benefit to modifying the protocol.

We decided to review our experience at the Hospital for Special Surgery (HSS), New York City, regarding MTX use in RA[7]. The ACR guidelines are widely accepted for general use among our rheumatologists and have been employed in our monitoring of MTX treatment. Our goal was to assess the utility of these guidelines for detecting MTX toxicity and the possibility that a change in this strategy could result in lower health care costs without increased risk to patients.

The HSS RA Registry and Repository contains data on 562 patients meeting the 1987 revised RA criteria[8]. We identified 222 patients who had previously taken or were currently taking MTX for their RA. Data from 40 patients were not available.

In our review of 182 patients (155 women, mean age 59.7 years, white 111, Hispanic 38, black 20, Asian 13) a total of 2791 LFT were performed, with 94 abnormal results. One hundred fifty-two patients (83.5%) with 2007 LFT evaluations had no abnormal results, compared with 30 patients (16.5%) who had at least one abnormal LFT in 784 tests. There was no statistically significant difference in patients who did and did not have LFT abnormalities with respect to age, sex, mean disease duration, current or prior DMARD use, or the frequency of blood test monitoring.

Twenty-two of the 30 patients (73.3%) with at least one LFT abnormality (highest AST 103 u/dl) continued treatment despite the elevation without further evaluation or change in therapy, and subsequent guideline directed LFT assessments were within normal limits. Two patients immediately discontinued MTX therapy following a single elevation in AST (within 2 times the upper limit of normal). Three patients with LFT abnormalities temporarily discontinued MTX (one patient with a history of alcohol dependence, one during total hip replacement, and one during concurrent antibiotic treatment). Upon resuming their previous MTX dose, LFT had returned to within normal limits in all 3 patients. A single patient with abnormal LFT was found to have similar abnormalities before the initiation of MTX; no change in MTX therapy or LFT was noted. Two other patients with abnormal LFT underwent 3 liver biopsies. The

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patient with 2 biopsies had had 2 consecutively elevated results (4 times the upper limit of normal), and both biopsies showed normal histology. The other patient underwent a liver biopsy as a result of an alkaline phosphatase finding greater than twice the upper limit of normal; this biopsy was also normal, but the patient did not restart MTX therapy.

While 3 patients experienced leukopenia during MTX treatment (lowest 2300/mm^3), only in one did this lead to discontinuation. The other 2 did not change their MTX dose and subsequent white blood cell evaluations were within normal limits.

Twenty-two patients had hypoalbuminemia during their MTX treatment (lowest 3.4 g/dl). Fourteen of these had had decreased albumin levels before MTX therapy and no clinically significant change while taking MTX. The remaining 8 patients had subsequently normal albumin levels without change in their MTX regimens.

One hundred twenty-eight patients (70.3%) continued taking MTX at the time of our analysis. Their mean MTX dose was 13.0 ± 5.5 mg/wk, with average duration of treatment of 37.9 ± 30.0 months. A total of 54 patients permanently discontinued MTX. Mean maximal MTX dose among these patients was 11.5 ± 3.7 mg/wk, with an average duration of treatment 19.4 ± 17.9 months. Other DMARD used by patients with no LFT abnormalities were hydroxychloroquine (n = 44), etanercept (n = 12), azathioprine (n = 8), leflunomide (n = 6), intramuscular (IM) gold (n = 4), sulfasalazine (n = 3), and penicillamine (n = 1). Among patients with LFT abnormalities, the other DMARD utilized were hydroxychloroquine (n = 5), azathioprine (n = 3), etanercept (n = 1), and IM gold (n = 1). Discontinuations of MTX were due to: inadequate response (n = 23); disease improvement (n = 3); gastrointestinal (n = 6), dermatologic (n = 5), pulmonary (n = 3) side effects; a new diagnosis of cancer (n = 3 breast, lung, and squamous epiglottis cancer); high LFT (n = 2); monocytosis (n = 1) or leukopenia (n = 1); increased intake of ethanol (n = 1); and hepatitis A (n = 1).

Table 1. Published studies utilized in the ACR recommendations.

Author	No. of Patients
Weinblatt[10*]	28
Weinblatt[17*]	26
Weinblatt[18*]	26
Kremer[13**]	29
Kremer[14**]	25
Kremer[15**]	18
Weinblatt[12†]	138
Weinblatt[16†]	89
Williams[11]	95
Furst[19]	45
Furst[20]	30
Total	549

*Same cohort. ** Same cohort, † Same cohort.

Five patients wished to discontinue treatment and did not specify a reason.

These impressive safety data led us to review the literature from which the original guidelines were drawn. During our review, we noticed some numerical discrepancies in the number of patients whose LFT data were used to develop the current guidelines. We were able to determine that the guidelines were actually based on 446 instead of 700 patients, of which 383 are in published studies[9-19] (Table 1). Eight of the 11 cohort studies were continuations of 3 separate investigations that had been reported previously. Individual subjects were counted multiple times as different patients, once for each separate publication. Thus, it is likely that the recommendations are based on a database with information gathered from a population in which many of the subjects have been included more than once, and this limits the power and generalizability of the data.

MTX has a well defined toxicity profile, and physicians monitor patients for gastrointestinal, hepatic and pulmonary toxicity, bone marrow suppression, and stomatitis. Hepatic toxicity has been noted in psoriasis patients using MTX for some time, and guidelines for monitoring hepatic toxicity have been published[20].

Since its initial use in the treatment of RA, the demographic and baseline profiles of those patients for whom MTX was prescribed have changed. Initially, MTX was reserved for patients who had climbed the RA treatment pyramid. These patients likely manifested complications due to both RA and the cumulative use of multiple toxic medications, as well as having other unrelated comorbidities that come with increasing age. More and more, MTX has been used earlier in the course of the disease. Patients are relatively healthier early in their disease and may be better able to tolerate possible side effects[21].

We believe the original cohort that was studied and that formed the basis for the current recommendations may not reflect the current group of patients using MTX. These guidelines were drawn from a cohort of RA patients who averaged more than 10 years of disease before they were enrolled in MTX trials, and failed multiple other DMARD before participating in RA trials. Patients with RA seen over the last decade might not meet the inclusion criteria that would lead to their enrollment in the DMARD clinical trials that generated the data used for the current guideline. This provides further evidence about the limitations in the use of data gathered solely from clinical trials[22]. Also, as with many guidelines, they signify a "best fit" based upon available data, often represent compromises, and demand updating when new data are available.

MTX is not only the DMARD most commonly used to treat RA, but is also the first prescribed, and the most common DMARD used alone or in combination treatments by most rheumatologists[1]. In our cohort, MTX seems to have very few clinically significant side effects. In contrast

to previous publications[5], discontinuation of MTX was mostly due to ineffectiveness rather than adverse effects. This provides further evidence that MTX may not be as hepatotoxic in patients with RA as formerly assumed. The frequent use of folic acid supplementation may be one of the factors contributing to the low incidence of side effects in this cohort, as noted[23]. The 5 year cumulative incidence of cirrhosis in RA patients treated with MTX has been calculated to be 1/1000[24]. Cirrhosis risk was increased in patients with psoriasis, diabetes, or alcohol use. It can be argued that the numbers of our patients were not high enough to yield one occurrence of cirrhosis; however, neither were the number of patients used in the guidelines. Both cohorts combined may not be sufficient to include one episode of cirrhosis of the liver. Our data reflect the experience of a single, urban, tertiary care center, thus potentially influencing the generalizability of our findings. Although we are also limited by the retrospective nature of our data, we believe and the authors of the current recommendations have noted that a prospective analysis of the question is not feasible due to the population size required, a low incidence of toxicity with MTX, and ethical considerations.

Our data do not provide an answer for the best frequency for LFT monitoring. One way to determine this would be to prospectively follow cohorts getting LFT evaluations at differing frequencies and to assess the safety of each different time interval protocol.

We suggest the following algorithm based on a responsible interpretation of our data. At initiation of MTX therapy, LFT should be checked in 6–8 weeks, per the current guidelines. If these are normal and the patient is taking a stable dose of MTX, then patients with no increased risk for liver problems (older age, alcohol dependence, multiple concurrent medical problems, especially diabetes, psoriasis, hepatitis) may be followed every 3–4 months. In case of a dose change, LFT should be monitored again every 6–8 weeks until a maintenance dose is reached. If any clinical signs or symptoms of liver problems are encountered (nausea, vomiting, right upper quadrant abdominal pain, icterus), then LFT should be repeated immediately and if abnormal, MTX should be stopped and the cause defined.

This small sample of patients, representing a fraction of the 250,000 patients presently using MTX in the USA, had 2791 LFT assessments over 14 years, at an estimated cost of $156,000 (utilizing the current direct charges at our institution for the tests recommended by the current guidelines). Consequently, less frequent liver function testing would decrease the cost of MTX monitoring, and would likely not place the patient at any increased danger of toxicity.

In view of our safety data, consideration for revision of the current MTX monitoring guidelines seems appropriate to reflect "new and compelling information" as suggested by the authors of the original recommendations[5] and others[25,26]. Based on longterm experience, less frequent monitoring, especially in patients without risk factors for liver disease, is both reasonable and responsible.

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