Methotrexate use in rheumatoid arthritis is associated with few clinically significant liver function test abnormalities

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ABSTRACT

Objective. To determine the frequency of liver function tests (LFT) abnormalities associated with methotrexate (MTX) use in the treatment of rheumatoid arthritis (RA).

Methods. A retrospective chart review for demographic information, RA-specific history, medication history, complications of therapy, results of all available blood tests (specifically aspartate aminotransferase (AST), alanine aminotransferase (ALT), complete blood count (CBC), albumin, creatinine), and liver biopsy reports was conducted for RA patients, who were currently using or have used MTX in the past.

Results. A total of 2791 LFTs were performed among 182 RA patients with 94 abnormal results. 152 patients (83.5%) with 2007 LFT evaluations demonstrated no abnormal results, compared with 30 patients (16.5%) who had at least one abnormal LFT in 784 tests. Twenty-two of the 30 patients with at least one LFT abnormality (73.3%) continued treatment despite the elevation without further evaluation or change in therapy, and subsequent LFT assessments were within normal limits. 128 patients (70.3%) demonstrated no abnormal results, compared with 30 patients (16.5%) who had at least one abnormal LFT in the past.

Conclusions. MTX appears to be associated with very few clinically significant hepatic side effects. In view of these data, consideration as to revision of the current MTX monitoring guidelines in the direction of less frequent monitoring, especially in patients with no risk factors for liver disease, may be considered.

Introduction

Methotrexate (MTX) is the most commonly prescribed disease modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA) (1).

In 1994, the American College of Rheumatology (ACR) published guidelines for monitoring the development of hepatic toxicity related to MTX (2). 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), and creatinine would also be performed at baseline. An editorial (3) questioned the necessity and cost effectiveness of routine monitoring of all RAPatients receiving second line agents for the development of hepatotoxicity and raised the issue of the potential benefit to modifying the current guidelines. Guidelines are often extrapolated from experience in previous studies, especially prospective investigations with pre-defined selection and outcomes criteria. The results do not always accurately reflect clinical practice or outcomes.

We performed a retrospective review of our experience with MTX use in 562 RA patients seen at our tertiary care institution. ACR guidelines are widely accepted for general use among our rheumatologists. Our goal was to determine the frequency of MTX-related LFT abnormalities.

Patients and methods

We identified 562 RAPatients followed at the Hospital for Special Surgery from 1985 to 1999. Of these patients 222 met the 1987 revised RA criteria (4), and they had previously taken or were currently taking MTX for their RA. The remaining 340 RA patients had not been on MTX. Patients were all identified through the RA Registry at HSS at the time. Patients were all seen by rheumatologists at the hospital. Forty of these patients were excluded because they had moved, changed physicians or had died. Age and disease duration of these patients were not statistically different from the remaining 182 patients. No deaths related to MTX use in this group were identified by the rheumatologists of these patients.

We recorded demographic information, RA-specific history, medication history, complications of therapy, results of all available blood tests (specifically the AST, ALT, CBC, albumin, creatinine), and liver biopsy reports from patient charts. Most of the blood tests were performed at our institution and recorded in a computerized database; the remaining blood test results were
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‡ p value: not significant; Mann-Whitney test;
‡‡ p value: not significant; Chi square test;
* p value < 0.05; Student’s t-test;
† taken from paper copies of the reports distributed by outside laboratories.

Results

Evaluation of LFT abnormalities

A total of 2791 LFTs were performed among the 182 RA patients (female 155, mean age 59, White 111, Hispanic 38, Black 20, Asian 13) with 94 abnormal results. One hundred and fifty-two patients (83.5%) with 2007 LFT evaluations demonstrated no abnormal results, compared with 30 patients (16.5%) who had at least one abnormal LFT in 784 tests. A comparison of baseline and disease characteristics between those RA patients who had at least one LFT abnormality and those whose LFTs were always within normal range is presented in Table I. There were no statistically significant differences between patients who did and did not have LFT abnormalities with respect to age, gender, or mean disease duration.

The frequency of monitoring among patients with an abnormal LFT, no abnormal LFTs and patients who have stopped MTX due to LFT abnormalities (Table I) was not different in any group (every 7.9 weeks, 8.2 weeks and 8.1 weeks, respectively).

MTX was the first DMARD used in 68 patients, 62 of whom remained on treatment at the time of this evaluation. Mean maximum MTX dose, and mean duration of MTX therapy, in patients with and without LFT abnormalities is shown in Table I. A total of 122 patients (68%) used folic acid concomitantly with their MTX. Differences in folic acid use between patients with no elevated LFTs and patients with at least one elevated LFT were not statistically significant.

Follow-up of patients with LFT abnormalities

Twenty-two of the 30 patients with at least one LFT abnormality (73.3%) continued treatment despite the elevation without further evaluation or change in therapy, and subsequent LFT assessments were within normal limits. Two patients immediately discontinued MTX therapy following a single elevation in AST. 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 doses, LFTs returned to within normal limits in all 3 patients. A single patient with abnormal LFTs was found to have similar abnormalities prior to the initiation of MTX; no change in MTX therapy or LFTs was noted. Two other patients with abnormal LFTs underwent 3 liver biopsies. The patient with 2 biopsies had had 2 consecutively elevated results (four times the upper limit of normal), and both biopsies demonstrated normal histology. This patient chose to continue MTX therapy despite continued laboratory abnormalities. The other patient underwent a liver biopsy as a result of an alkaline phosphatase of greater than twice the upper limit of normal; this biopsy was also normal, but the patient did not restart MTX therapy.

Evaluation of other laboratory abnormalities

Three patients experienced leukopenia during MTX treatment (lowest 2,300). Only one of these patients discontinued MTX as a result. The other 2 did not change their MTX dose and subsequent WBC evaluations were within normal limits. Twenty-two patients demonstrated hypoalbuminemia during their MTX treatment (lowest 3.4 g/dl). Fourteen of these had had decreased albumin levels prior to MTX therapy with no clinically significant change following drug initiation. The remaining 8 patients had subsequently normal albumin levels without change in their therapeutic regimens with regard to MTX.

Discontinuation of MTX

One hundred twenty-eight patients (70.3%) remained on MTX at the time of our study. Their mean MTX dose was 13.0 ± 5.5 mg/wk with an 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 of 19.4± 17.9 months.

The most common reason for discon-
Discussion

MTX has a well-defined toxicity profile and physicians monitor patients for gastrointestinal, hepatic, and pulmonary toxicity, bone marrow suppression and stomatitis, and guidelines for monitoring hepatic toxicity have been published (5). MTX was initially used in psoriasis before RA, where it was noted to have hepatic toxicity, which led to guidelines for liver biopsies to monitor toxic effects. However, there appears to be important differences between psoriasis and RA in the toxicity of MTX, which may be due to biological differences in patient populations. Since its initial use in the treatment of RA, the demographic and baseline profiles of those patients for whom MTX was prescribed has changed. Initially, MTX was reserved for those patients who had climbed the RA treatment pyramid. 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 (6). Older cohorts of RA patients, who had failed multiple other DMARDs before participating in RA trials undoubtedly 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. This further distinguishes the current MTX-treated population from the cohorts examined previously. MTX also has a different toxicity profile when used in high doses for cancer chemotherapy compared to the low doses used for RA treatment. At this time because of its efficacy and safety profile, MTX is considered the anchor DMARD in the treatment of RA(7).

In our cohort, MTX appears to have very few clinically significant side effects. In contrast to previous publications (2, 8) discontinuation of MTX was primarily due to ineffectiveness rather than adverse effects. This finding provides further evidence that MTX may not be as hepatotoxic as assumed in the literature (9-14). 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 previously noted in the literature (15).

The low incidence of abnormal LFTs could be said to be a result of already following the guidelines at our institution. However, even when this is true, if there was a true and significant increase in abnormalities these would have been identified; actually would have been more likely to be identified because of the frequent, maybe unnecessarily so, monitoring. However, even when abnormalities were noted no action was taken on the part of the clinician to change the way they were using MTX. Testing per se would not normalize an elevated LFT. The reality in our experience remains that LFT abnormalities are very rare and when they do occur they are clinically not significant.

We have no data about non-steroidal anti-inflammatory medication (NSAID) use in all patients. Even if we assume these patients used no NSAIDs, LFT abnormalities on only MTX are very few. In reality most of these patients were using NSAIDs at least part of the time, which adds more strength to our argument that MTX causes few LFT abnormalities.

Our data do not provide an answer as to what would be the best frequency for LFT monitoring. However, these findings suggest that a less frequent monitoring may be reasonable, as hinted at in a recent study of a survey of rheumatologists (16). The best way to determine this would be to prospectively follow cohorts getting LFT evaluations at differing frequencies, which may be unlikely in the current rheumatology research environment.

We would suggest the following algorithm based on a responsible interpretation of our data. At initiation of MTX therapy, LFTs should be checked in 4-8 weeks, as per the current guidelines. If these are normal and the patient is on a stable dose of MTX, then patients with no increased risk for liver problems (older age, multiple concurrent medical problems, hepatitis) may be followed every 3-4 months. In case of a dose change, LFTs should be monitored again every 4-8 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 monitoring as the current guidelines suggest is recommended.

Our study reflects the experience of a single, urban, tertiary care center, thus possibly influencing our findings. We have tried to give the situation in a real world setting. Although this study is limited by its retrospective nature, the authors of the current recommendations have noted that a prospective analysis of the question is not feasible due to population size required, low incidence of toxicity with MTX, and ethical considerations. Recent studies of RA patients have documented the necessity for real-world observational studies as a complement to randomized controlled trials, as prospective trials have limited generalizability (17). There are data to support our findings from other patients cohorts, showing LFT abnormalities on the ranges of commonly used non-steroidal anti-inflammatory medications (18).

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 costs at our institution for the tests recommended by the current guidelines). Consequently, less frequent LFT 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 as to revision of the current MTX
monitoring guidelines in the direction of less frequent monitoring, especially in patients with no risk factors for liver disease, may be in order.

References