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Measuring Transaminases in Patients with Rheumatoid Arthritis on Weekly Methotrexate: Does Timing of Blood Testing Matter?

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Abstract

Introduction—The change in transaminase levels over a single week during therapy with methotrexate (MTX) has not been investigated or reported to date. In clinical practice, it is common to observe abnormal transaminase levels upon routine blood work for toxicity monitoring. Many have suggested that such lab abnormalities can sometimes be attributed to sampling blood for toxicity monitoring proximately following MTX dosing. The aim of our study was to evaluate changes in transaminase levels (AST/ALT) over one week after MTX administration in rheumatoid arthritis (RA) patients.

Methods—In this small proof of concept study we evaluated 13 patients with RA taking stable doses of methotrexate and background medications (e.g. NSAIDs, prednisone), but no other disease-modifying anti-rheumatic drugs (DMARDs). All patients were on a stable dose of folic acid. Patients received their usual doses of MTX administered at a specified time, and then sequential blood samples were obtained over the course of 7 days. Peripheral blood was obtained at each time point to measure serum transaminases.

Results—We did not observe any significant change in sequential transaminases over 1 week in relationship to MTX administration.

Conclusion—In this small study, we did not observe change in transaminases in relationship to methotrexate administration. It is possible that MTX therapy alone does not lead to significant weekly transaminase variations, contrary to our clinical expectations. The addition of other medications (i.e. NSAIDs) to stable MTX regimen may result in transaminase abnormalities.

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Conflicts of Interest

The authors declare they have no conflicts of interest. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors agree to allow the journal to review their data if requested.

Ethics Approval and Consent to Participate

The study was approved by the Johns Hopkins Institutional Review Board, and all patients provided written informed consent.

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Author Contributions

All authors were involved in designing the study, analyzing the data, drafting the article, or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bingham had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Keywords

rheumatoid arthritis; methotrexate; pharmacology; transaminases

INTRODUCTION

Methotrexate (MTX) is the current cornerstone of pharmacological management for most patients with rheumatoid arthritis (RA) and many other forms of inflammatory arthritis. Low-dose MTX was first demonstrated to be a potent and effective therapy in RA and continues to be the mainstay of treatment due to its efficacy, acceptable safety profile, and low cost.

The 2015 ACR recommendations for the use of DMARDs in RA support the use of MTX as the first line therapy for most patients[1]. Similarly, according to recent EULAR recommendations for management of RA based on broad systematic literature review, MTX should be part of the first treatment strategy for patients with active RA[2].

Early prospective studies of MTX in patients with RA reported that its use was accompanied by an increase in liver function tests, specifically aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[3]. In one study, transaminase elevations of greater than twice normal levels occurred in 31% of patients and developed exclusively within the first 18 months of therapy[4]. In another study, the likelihood of observing an increase in AST or ALT in RA patients taking MTX was 13-fold and 15-fold, respectively, compared to patients taking placebo[5]. A systematic literature review of the long-term safety of MTX monotherapy in RA revealed 20% of patients had at least one episode of transaminase elevation, 13% had an elevation up to two times the upper limit of normal, and 3.7% of patients stopped MTX because of liver toxicity[6].

Notably, there are numerous other factors that have been reported to affect transaminase levels during treatment with MTX. The lack of adequate folic acid supplementation, use of concurrent medications such as non-steroidal anti-inflammatory drugs (NSAIDs), other disease-modifying anti-rheumatic drugs (DMARDs), alcohol consumption, elevated BMI or untreated hyperlipidemia may expose patients receiving MTX to a higher risk for transaminase elevations[7].

Most published studies have focused on MTX toxicity and transaminase changes over long periods of time. However, the change in transaminase levels over a single week during therapy with MTX has not been investigated or reported to date. In clinical practice, it is common to observe abnormal transaminase levels upon routine blood work for toxicity monitoring. Many have suggested that such lab abnormalities (which oftentimes revert to normal on repeat testing) can sometimes be attributed to sampling blood for toxicity monitoring proximately following MTX dosing. For example, an elevated AST found on Tuesday blood sampling when a patient took methotrexate the day before on Monday could be attributed to proximate MTX administration more so than an abnormal lab on Friday. We wished to explore whether LFT elevations could be demonstrated with sequential testing over a week following MTX administration.

MATERIALS & METHODS

In this small proof of concept study, 13 subjects with RA were recruited from Johns Hopkins Arthritis Center and Rheumatology Clinics. Ten subjects were enrolled in 2011 and an additional three in 2015. The study was approved by the Johns Hopkins Institutional Review Board, and all patients provided written informed consent. All participants were age 18 and older and met 2010 ACR-EULAR Classification Criteria for RA (8).

All participants were taking MTX for at least three months and on the same dose for at least four weeks prior to study enrollment. Other background medications (e.g. NSAIDs, prednisone) were kept at their baseline doses, with no titration permitted during the study period. Additional DMARDs were not allowed during and two months prior to the study. All subjects were on stable background doses of folic acid (1 mg/d), with no patients receiving concomitant folinic acid.

In order to standardize the timing of MTX administration, after enrollment, all participants were asked to change their MTX dosing to Monday mornings for the following 2 weeks. The baseline study visit occurred the 3rd Monday after switching MTX dosing. During that visit blood was obtained for transaminase determination, and the time of blood collection was recorded. MTX was then administered under observation. The patient was seen at 3 subsequent visits over the next week (Baseline + 1 day, Baseline + 4 days, Baseline + 7 days) at approximately the same time of the day for blood sampling. At each visit concomitant medications taken and dose changes were captured. At the completion of the study all patients resumed their regular pre-study therapeutic schedule and follow up care. Serum transaminases (ALT, AST) were evaluated at the Johns Hopkins Clinical laboratory by photometric analysis using Siemens Vista 1500 Intelligent Lab System. Summary statistics were performed in Microsoft Excel and Stata v14.0. Trend lines were plotted for individual patients over time.

RESULTS

A total of 13 subjects successfully completed the study. Summary baseline demographics and disease characteristics is provided in Table I.

Variability and changes in ALT and AST over one week period of time were summarized and compared (Figures 1a and 1b). There were no significant fluctuations or temporal changes in the level of transaminases in regards to the timing of MTX administration over a week period. The transaminase level variability was in the range of 5 U/L during the course of the study. In none of the participants did ALT or AST reach a level of two times the upper limit of normal (ULN), even in 2 patients who had baseline ALT levels ~1.2× the ULN, although in these 2 patients somewhat greater changes were seen over the course of the week (approximately 10 U/L).

Factors such as demographics, RA disease duration, seropositivity, MTX dose, and recent alcohol intake did not affect the transaminase levels over a period of one week. Concomitant steady low-dose steroid or NSAID intake along with the stable dose MTX also did not affect the transaminase levels. However, in one patient (Patient *) who inadvertently introduced

ibuprofen 800 mg/day after the second visit, there was an upward trend in transaminase levels noted.

DISCUSSION

Methotrexate administered weekly for the treatment of RA and other forms of inflammatory arthritis requires periodic monitoring of transaminases and blood counts for potential toxicity[9]. In clinical practice, increased transaminases are occasionally encountered, but often become normal on repeat testing with no intervention.

Laboratory monitoring of patients on MTX therapy is essential to reduce the risk of unrecognized serious liver disease. ACR guidelines published in 1994 indicate that AST, ALT and albumin levels should be monitored every 4–8 weeks in patients on stable dose of MTX[5]. Current ACR recommendations for monitoring suggest initially monitoring transaminases every 2–4 weeks, then every 12 weeks in patients on stable therapeutic doses[1]. Visser et al published multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis[10]. On the basis of systematic literature research and expert opinion, 10 multinational key recommendations on the use of MTX were formulated. Among these, transaminases should be monitored every 1–3 months when a stable dose of MTX is reached and more frequently initially when adjusting the dose. MTX should be stopped if there is confirmed increase in ALT/AST greater than 3 times ULN, but may be reinstituted at a lower dose following normalization. If the ALT/AST levels are persistently elevated up to three times the ULN, the dose of MTX should be adjusted; diagnostic procedures should be considered in the case of persistently elevated ALT/AST more than three times the ULN after discontinuation.

For RA patients the evidence suggests that liver enzyme elevation is frequent but often transient. MTX is commonly continued without a dose change, but the frequency of spontaneous normalization is insufficiently reported.

We had previously documented several occasions in our daily clinical practice when patients taking MTX were found to have abnormally elevated transaminases above 2 times ULN. When we looked back at the timing of their lab work draw and MTX intake, we suspected that MTX taken immediately before lab sampling could be the culprit of this transaminase elevation. On repeated testing, transaminases would often return to their baseline, and no change in therapy was needed.

Based on our clinical observations, we hypothesized that blood testing immediately following MTX may be associated with increased transaminases. We conducted this small study to determine if we could provide evidence for a MTX timing-related transaminase increase. In our study of 13 participants we did not see any significant transaminase changes.

A limitation of this study was our small sample size, which is inadequate to make any final conclusions. Because of the small sample size and the reported rates of transaminase elevations with MTX, it is possible that we had a type II error. Because we did not observe any change in transaminases in most patients, it is impossible to determine if clinical factors were responsible. It is however of interest that the single patient who had a notable increase

in ALT (approximately 20 U/L) above baseline took ibuprofen during the week of the study, and this same patient also had a rise of approximately 10 U/L in AST.

Our study benefits from comparing changes in transaminase levels in individual patients over time relative to their baseline, instead of a more traditional population-based pharmacokinetic/pharmacodynamic study that may require much larger numbers of patients. For this preliminary study, the data is significant in its novelty in determining the variability and in informing future studies. Because the variability is not known, and this is a pilot study, a power calculation was not performed. It is possible that with a larger sample size the chance of capturing transaminase abnormalities would be higher and more successful.

Overall, this study suggests that the day of the week may not be relevant when monitoring methotrexate toxicity lab work. It is possible that in our daily practice occasional elevations of transaminases in patients on MTX could sometimes be attributed to newly added or as needed use of other medications (i.e. NSAIDs, antibiotics, other DMARDs), and the vigilant physician should look for this possibility before adjusting the dose of MTX. Given that we did see some variability in levels over time after MTX administration, repeating an abnormal lab for confirmation is warranted before necessarily altering MTX dosing.

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Figure 1.

1a and 1b. AST (Figure 1a) and ALT (Figure 1b) Levels over 4 visits, during a one week period of time. D0 corresponds to baseline before MTX administration, D+1: one day after, D+4: four days after D+7: seven days after. ULN=upper limit of normal. Laboratory reference range for AST: 10 – 40 U/L; ALT: 9 – 46 U/L. Patient * started ibuprofen 800mg/d D+1.

Table I

Baseline patient demographics and disease characteristics. Values are the mean $\pm$ standard deviations where applicable.

Age, years	57.9 $\pm$ 11.2
Female sex, %	66
Ethnicity - Caucasian/ African American/Other, %	53/31/16
Disease duration, years	8 $\pm$ 5.8
RF positive, %	54
CCP positive, %	62
Methotrexate dose, mg/week	18.9 $\pm$ 4.9
Alcohol consumption-days in last 1 month / drinks during those days	2.3 $\pm$ 3.4 / 0.7 $\pm$ 1
BMI	30 $\pm$ 5.8
NSAID use, %	33
Steroid use, % / dose (mg/d)	31 / 7.3 $\pm$ 5.2