Editorial

Not Yet Time to Change the Guidelines for Monitoring Methotrexate Liver Toxicity: They Have Served Us Well

Methotrexate (MTX) use in patients with psoriasis may be associated with considerable hepatotoxicity[1-3]. Liver biopsies were therefore recommended after a patient had achieved a mean cumulative dose of MTX of 1.5 g, and then again after each additional 1 g[4]. Testing of liver transaminase enzyme levels was thought to be of no value in predicting the development of clinically significant liver disease (CSLD)[4].

Because of the reports of liver disease associated with the use of MTX in psoriatic patients, rheumatologists recognized the need to assess hepatic safety in patients taking MTX for the treatment of rheumatoid arthritis (RA). With the more widespread use of MTX in the 1980s, the issue of determining the hepatic safety profile of the drug in this group of patients came into sharp focus.

The early prospective studies of MTX in patients with RA confirmed that its use was accompanied by some increase in hepatic transaminase enzymes[5]. The implications of these abnormalities were unclear until prospective studies could be performed in which frequent monitoring of the enzyme abnormalities could be correlated with actual biopsy samples of hepatic tissue. When this was done, it became possible to examine the relationship between the abnormalities of blood testing of transaminase enzymes and serum albumin with the actual evaluation of changes of hepatic architecture.

With the analysis of liver blood tests and liver biopsy tissue obtained, certain clinically useful relationships emerged. Contrary to the doctrine that hepatic changes in patients with psoriatic arthritis could not be predicted by abnormalities in liver enzymes[1-4], it became apparent that there was indeed a significant correlation between hepatic aspartate aminotransferase (AST) and progression of histologic deterioration in patients with RA receiving chronic weekly MTX[6]. The disparity between the seemingly conflicting data in patients with psoriasis and RA was resolved when the methodology of blood sampling was examined more closely. The psoriatic patients had blood sampling for determination of enzyme levels on the day of the biopsy[1-3], while the patients with RA underwent frequent and regular blood monitoring at regular intervals between liver biopsies[6].

Examination of the results of sequential liver biopsies in patients with RA who were managed to keep the hepatic AST and serum albumin within the normal range while avoiding all alcohol actually revealed some improvement in hepatic histology over prolonged periods of MTX exposure[7,8]. It therefore became apparent that liver toxicity was not necessarily an inevitable outcome of longterm MTX treatment[9].

The pattern of increase of transaminase enzymes, which actually correlated with hepatic damage seen at the time of liver biopsy, was of interest. *Any* elevation of serum AST into the abnormal range was predictive of hepatic histologic deterioration[6]. This made sense considering that the mean value of AST in patients with RA taking MTX more than doubles from baseline values, even while remaining in the normal range[10] (Figure 1). This observation, along with the consideration that the laboratory defined upper limit of normal is 2 standard deviations from the norm, lends further credibility to the finding that any increase in AST values into the abnormal range may be associated with liver damage, and led to the recommendations in the American College of Rheumatology guidelines published in 1994, which indicate that the MTX dose should be adjusted to keep the transaminase enzyme values within the upper limit of normal[11]. The utility of these recommendations has been validated by others[12], and they have generally served us well. MTX hepatotoxicity has evolved from a primary concern limiting drug use into a secondary concern because of the infrequency of CSLD in the very large number of patients with RA receiving the drug around the world.

It would therefore be ironic if the reason for the drastic decrease in MTX induced liver toxicity became the driving

See Monitoring for MTX hepatic toxicity in RA: Is it time to update the guidelines? *page 1586*

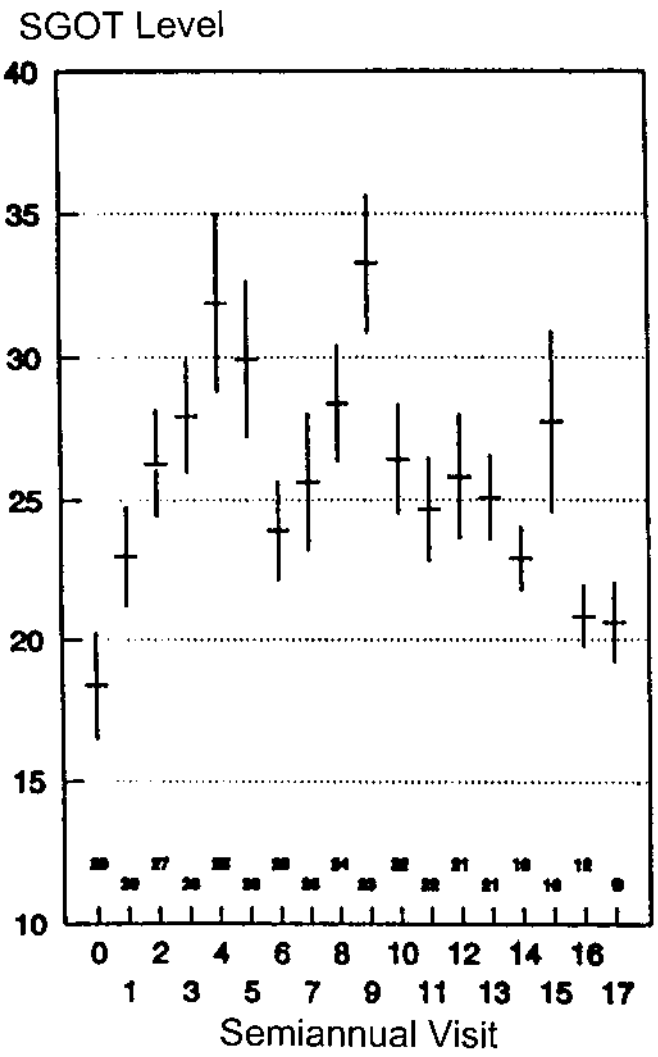

Figure 1. Mean (± SEM) levels of serum aspartate transaminase (AST; IU/l) over time in a cohort of 29 patients receiving longterm methotrexate (MTX) therapy[14]. It should be noted that the mean AST level doubled between baseline and semiannual visit 9 (54 mo), when the cohort was receiving a mean (± SEM) MTX dosage of 14.6 ± 4.2 mg/week. The mean AST level decreased thereafter through semiannual visit 16, when the MTX dosage had been reduced to 11.7 ± 6.6 mg/week. The difference in mean AST level from baseline was significant at week 16 ($p = 0.0001$) and the value at visit 9 was significantly different from that at visit 16 ($p = 0.03$). Note that although mean AST values increased significantly, they remained within the accepted "normal" range. Numbers inside the lower portion of the box are the number of patients tested at each visit; a total of 768 measurements were made. Horizontal portions of crossbars are the mean; vertical portions are the SEM. From Kremer JM, Koff R, with permission[10].

force behind a movement to relax the vigilance with which hepatic enzymes and serum albumin are monitored. The rationale for the final recommendation of blood sampling at intervals of 4 to 8 weeks was derived from an analysis of the percentage of the increases of AST into the abnormal range that would be missed if monitoring were to occur at less frequent intervals. Blood sampling at intervals of 90 days would actually miss 68% of all elevations of AST compared with samples obtained every 45 or 60 days, which result in missing 17% and 41%, respectively[11] (Table 1). MTX patients do indeed exhibit an increased evidence of transaminase enzyme elevations compared with control patients. "The likelihood of finding an increase in AST or ALT in RA patients taking MTX was 13 fold and 15 fold, respectively, greater than in patients taking placebo ($p < 0.0001$ for both comparisons)"[11].

To my knowledge, there has only been one case of CSLD in a patient with RA receiving MTX in whom the frequency of monitoring of AST and serum albumin was performed as per the published guidelines, and the weekly dose of MTX was adjusted in order to keep these values within the normal range. This was in an insulin dependent diabetic[12]. It is possible that the published guidelines are less effective in this population, although no other reports of this association have emerged.

The experience at The Hospital for Special Surgery (HSS) described in the accompanying editorial in this issue of *The Journal* may not be at all atypical[13]. What is not entirely clear from their retrospective chart review is whether the skilled clinicians at their institution managed patients specifically to avoid abnormalities in transaminase enzymes and serum albumin during the period covered by their review. If this was the case, as it has been nationally for the past 8 years, this practice would have influenced the frequency of the abnormalities they, and others elsewhere, observe. The HSS patients may also differ from the patients analyzed for the guidelines in several other clinically relevant ways. First, the published guidelines cohort was actually younger than the HSS cohort (mean age of 54 compared with 59.7 in the HSS patients), which might be expected to result in less hepatotoxicity, not more. Second, the mean weekly dose of MTX was only 13.0 mg in the HSS patients compared with 14.6 mg in the cohort from which most of the sequential liver biopsies were derived[14].

As the clinical response to MTX is dose dependent[15], it is therefore likely that the relatively low weekly dose of the drug would account for their observation that the most common reason to discontinue MTX in their cohort was lack of efficacy rather than toxicity. As the HSS authors note, their experience in this regard is different from that of

Table 1. Probability of missing a random elevation of the aspartate aminotransferase (AST) level, according to the frequency of blood sampling.

Blood Sampling Frequency, days	Probability of Missing an Elevation of AST, %
30	9
45	17
60	41
90	68

From Kremer JM, *et al*, with permission.

most others[14-18]. In an era when rheumatologists are adding expensive and potentially toxic drugs to MTX, it is reasonable to derive the maximum possible therapeutic effect from the drug and this will inevitably mean higher doses[19].

As MTX weekly dosing is associated with reduced hepatic folate stores[20], patients would be theoretically susceptible to a greater potential for liver toxicity with the higher doses needed to achieve the greater therapeutic benefit. It is also likely that we have reduced the incidence of liver toxicity and transaminitis further by the routine prophylactic use of folate supplementation. It is possible that the more commonplace utilization of folate also accounted for a relative decrease in the frequency of abnormalities they observed. It may also account for the relatively steep dropoff of the frequency of abnormalities in liver blood tests after the first two years observed in the cohorts cited in the published guidelines, as folate supplementation became more commonplace.

If one were to significantly reduce the interval used to monitor hepatic laboratory values as suggested, what would replace the existing system? It is unlikely that human biology would have changed significantly in the few decades since the initial reports of CSLD with MTX use[1-3]. It would make little sense to forgo blood testing for the previously discredited and abandoned system of regularly performed surveillance liver biopsies. The costs associated with the procedure as well as the inevitable, although rare complications, are considerable[11].

The published guidelines are based upon sound defensible evidence that has served patients and their physicians well. They are, nevertheless, not sacred and should be revised in the event of credible new evidence of an alternative strategy to assess the very real potential for liver damage with MTX. New data should include actual descriptions of liver histology obtained at the time of biopsy, rather than only blood tests with no indication of their relevance to the actual outcome of concern. In the absence of this kind of rigorous data, it makes little sense to alter the present guidelines.

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