GUIDELINES FOR ROUTINE LIVER BIOPSY DURING METHOTREXATE TREATMENT

■ *To the Editor:* We would like to commend Dr. Brass for his excellent review of the hepatic toxicity of antirheumatic drugs.[1] Dr. Brass correctly points out that the issues surrounding routine biopsies in methotrexate-treated patients are controversial. However, we feel that the accumulated data on this subject allow for the establishment of clearer guidelines than those stated in the review.

Several lines of evidence argue strongly against performing liver biopsy *routinely* in methotrexate-treated rheumatoid arthritis patients.

First, methotrexate hepatotoxicity appears to be much less of a problem in rheumatoid arthritis patients treated in the 1980s and 1990s than it was in psoriatic patients treated in the 1960s or 1970s. A recent survey of members of the American College of Rheumatology estimated that the risk of serious liver disease in methotrexate-treated rheumatoid arthritis patients was approximately one in 1000.[2] Long-term follow-up of methotrexate-treated rheumatoid arthritis patients has shown that the drug can be tolerated for prolonged periods of time without the development of cirrhosis.[3,4] The reason for this discrepancy may be that patients treated at later dates were more forcefully warned about alcohol use and were screened for known risk factors of methotrexate hepatotoxicity such as pre-existing liver disease and reduced renal function. In addition, rheumatoid arthritis patients have generally been treated with lower weekly doses of methotrexate than the psoriasis patients referred to in previous studies, and once-daily therapy has been discouraged. Other factors that may have improved the hepatic safety of methotrexate in rheumatoid arthritis include the simultaneous use of hydroxychloroquine[5] and folate supplementation.[6] Incidentally, a recent study of psoriatic arthritis patients treated in the 1980s and 1990s using these guidelines was remarkable for the lack of demonstrable hepatotoxicity.[7]

Second, as Dr. Brass points out, liver biopsy is expensive and invasive. Death and serious morbidity has been reported in rheumatoid arthritis patients undergoing routine liver biopsy.[8,9]

Third, an analysis recently presented at the 1993 American College of Rheumatology meeting in San Antonio has seriously questioned the cost-effectiveness of screening liver biopsies in methotrexate-treated patients.[10] The authors estimated a cost of $1 million per case of serious liver disease found (assuming a prevalence of serious liver disease of 0.1% in treated patients); 150 liver biopsy complications were estimated per 100 cases of serious liver disease found.

Fourth, there is little evidence that routine liver biopsy yields data that can be rationally used to alter therapy. Two patients reported with methotrexate-induced severe liver disease underwent three biopsies each, all before their disease developed.[11] Many biopsies will show fatty change, inflammation, or fibrosis without cirrhosis, which has been seen in rheumatoid arthritis patients never exposed to methotrexate.[3,12,13] Consensus has not been reached regarding the prognostic implications of these histologic findings.

Liver biopsy should not be performed as part of an arbitrary protocol in rheumatoid arthritis patients taking methotrexate. Clinicians treating patients with methotrexate should obtain liver biopsy specimens prior to institution of methotrexate only if there is reason to suspect pre-existing chronic liver disease. Sustained elevations of liver function tests, declining serum albumin, suspected surreptitious alcohol intake, or other factors that suggest that liver disease may have developed during therapy may justify periodic biopsy.

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■ *Reply:* Drs. Cash and Wilke provide a useful extension of the concepts in my review. I completely agree with their assessment of this issue, and thank them for drawing the conclusion in a less ambiguous manner than I. The desire to be able to do something about a clinical problem (ie, prevent serious methotrexate-induced hepatotoxicity) is an insufficient rationale for the routine use of an expensive procedure associated with significant morbidity (ie, liver biopsy) in the absence of data demonstrating the clinical usefulness of the procedure.

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