



## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> 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<sup>5</sup> and folate supplementation.<sup>6</sup> 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.<sup>7</sup>

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.<sup>8,9</sup>

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.<sup>10</sup> 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.<sup>11</sup> Many biopsies will show fatty change, inflammation, or fibrosis without cirrhosis, which has been seen in rheumatoid arthritis patients never exposed to methotrexate.<sup>3,12,13</sup> 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 biopsies.

JOSEPH M. CASH, MD, AND  
WILLIAM S. WILKE, MD  
Department of Rheumatic  
and Immunologic Disease  
The Cleveland Clinic Foundation

---

### REFERENCES

1. Brass EP. Hepatic toxicity of antirheumatic drugs. *Cleve Clin J Med* 1993; 60:466-472.
2. Walker AM, Funch D, Dreyer NA, et al. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. *Arthritis Rheum* 1993; 36:329-335.
3. Kremer JM, Lee RG, Tolman KG. Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy. A prospective study with baseline and sequential biopsy samples. *Arthritis Rheum* 1989; 32:121-127.

4. **Aponte J, Petrelli M.** Histopathologic findings in the liver of rheumatoid arthritis patients treated with long-term bolus methotrexate. *Arthritis Rheum* 1988; **31**:1457-1464.
5. **Fries JF, Singh G, Lenert L, Furst DE.** Aspirin, hydroxychloroquine, and hepatic enzyme abnormalities with methotrexate in rheumatoid arthritis [see comments]. *Arthritis Rheum* 1990; **33**:1611-1619.
6. **Kremer JM, Galivan J, Streckfuss A, Kamen B.** Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients. Association with hepatic folate deficiency and formation of polyglutamates. *Arthritis Rheum* 1986; **29**:832-835.
7. **Espinoza LR, Zakraoui L, Espinoza CG, et al.** Psoriatic arthritis: clinical response and side effects to methotrexate therapy. *J Rheumatol* 1992; **19**:872-877.
8. **Cash JM, Swain M, Di Bisceglie AM, Wilder RL, Crofford LJ.** Massive intrahepatic hemorrhage following routine liver biopsy in a patient with rheumatoid arthritis treated with methotrexate. *J Rheumatol* 1992; **19**:1466-1468.
9. **McGill DB, Rakela J, Zinsmeister AR, Ott BJ.** A 21 year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology* 1993; **99**:1396-1400.
10. **Alarcon GS, Lightfoot RW, Kremer JM, et al.** Selective vs unselective liver biopsies in methotrexate (MTX)-treated rheumatoid arthritis (RA) patients [abstract]. *Arthritis Rheum* 1993; **36**:S64.
11. **Clegg DO, Furst DE, Tolman KG, Pogue R.** Acute, reversible hepatic failure associated with methotrexate treatment of rheumatoid arthritis. *J Rheumatol* 1989; **16**:1123-1126.
12. **Rau R, Karger T, Herborn G, Frenzel H.** Liver biopsy findings in patients with rheumatoid arthritis undergoing long term treatment with methotrexate [see comments]. *J Rheumatol* 1989; **16**:489-493.
13. **Webb J, Whaley K, MacSween RNM, Nuki G, Dick WC, Buchanan WW.** Liver disease in rheumatoid arthritis and Sjögren's syndrome. *Ann Rheum Dis* 1975; **34**:70-79.

■ **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.

ERIC P. BRASS, MD, PhD  
Assistant Director  
California Clinical Trials Medical Group  
Beverly Hills



## INVITATION TO AUTHORS

**A**UTHORSHIP in the *Cleveland Clinic Journal of Medicine* is open to physicians everywhere, and we invite you and your colleagues to submit your manuscripts for publication. More than 80,000 physicians receive the *Journal*, and they look to the publication as a reliable source of scientific and clinical information.

The *Journal* is a peer-reviewed general medical journal published since 1932. It is published by the Cleveland Clinic Educational Foundation as part of its program of medical education and scientific communication. The publication's objective is to disseminate scientific and clinically significant information to the medical community, especially physicians in practice.

Please send your manuscript to:  
Herbert P. Wiedemann, MD, Editor  
CLEVELAND CLINIC JOURNAL OF MEDICINE  
EE37  
9500 Euclid Avenue  
Cleveland, Ohio 44195  
Phone (216) 444-2661; fax (216) 444-9385

---

### TYPES OF ARTICLES

---

#### Original study

Report of original investigation

#### Comprehensive review

In-depth analysis of subject relevant to medical practice, such as diagnosis and treatment of disease and clinical implications of research

#### Brief review

Article that addresses a discrete clinical problem and reflects the author's expertise

#### Editorial

Timely commentary on a controversial issue