Is Liver Biopsy Necessary During Low-dose Methotrexate Therapy? A Comment to the Hepatologist's View

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Although we in general agree with the hepatologist's view we do have some comments to the article of Christensen (1) in the February issue of this journal. We would like to emphasize that we have been among the first to suggest it was time to reconsider the standard use of liver biopsies (2) during methotrexate (MTX) therapy for psoriasis, and have a new article in press on this subject (3). The two main reasons for a reappraisal have been the appearance of new non-invasive tests and reports on less frequent appearance of MTX-induced fibrosis and cirrhosis (2, 3).

In the historical part of his article, Erik Christensen mentions reports that show that up to 26% of patients with psoriasis developed cirrhosis on MTX as a main reason for the intensive monitoring using regular liver biopsies. This high incidence, which was published by us in 1980 (4), is, as has been the case, reported without mentioning that the 25.6% belongs to a subgroup of 39 patients all treated for more than five years and having passed a cumulative dose of 4 g, while the study as a whole contained 183 patients treated with <4 g including 96 treated from one to five years. For the whole study the frequency was 10.3%, which still represents a highly significant hepatotoxicity. We also reported that eleven of the 39 patients had previously been on arsenic and vitamin A, and that five of the 39 patients admitted later, previously have had a heavy alcohol intake. All had a normal pretreatment liver biopsy, but according to our present view approximately one third belong to risk groups. They were unfortunately not studied with gammaglutamyltransferase. It should be noted, that data from Nyfors from the Finsen Institute in Copenhagen (5) were very close to ours.

Almost all patients, which had received arsenic and vitamin A got it from a single general practioner, who for many years treated patients with psoriasis from all over Denmark with this combination (6). We agree, that our data may have been important for promoting the "liver scare", but the background for the guidelines formulated by Roenigk and co-workers were not these figures but data from a large international study group, which evaluated 242 liver biopsy specimens in 1973 (7) and more than 1000 in 1976 (8). These data showed that cumulative dosage, increased alcohol intake, and the combination of diabetes and obesity, were associated with liver damage.

We believe that liver biopsies should be assessed by an experienced histopathologist and for all our studies mentioned have used the same (one of us). The evaluations were based upon gradings from 1 to 4 for steatosis, nuclear variability, peri-portal inflammation, focal necrosis and fibrosis. When following cirrhosis, cumulative figures representing total scores for fibrosis, judgment of membrane limitans, destruction and regenerations were used. For the sake of continuity, we have kept to this evaluation in spite of the later introduced various newer semiquantitative classifications mentioned by Christensen. The classification of cirrhosis has been the same as his.

Christensen refers to the article by Aithal et al. (9) from 2004, who used Ishak and Scheuer scales, to support that hepatic fibrosis does not increase significantly with the cumulative MTX dose in psoriasis, however the authors actually show that among their 121 biopsies from 66 subjects, the cumulative probabilities of advanced fibrosis were 0%, 2.6%, 2.6%, 8.2% and 8.2% at cumulative MTX.doses of 1.5, 3.0, 4.5, 5.0 and 6.0 g.

We are happy to learn, that there is a general acceptance, that most cases of chronic liver diseases including alcoholic cirrhosis have the potential to revert toward a more normal function. Christensen adds that in MTX toxicity there is also evidence of some reversibility of liver fibrosis after discontinuation of the drug. When we published our data on serial biopsies in 25 patients with MTX-induced cirrhosis (6) in 1980 and showed that cirrhosis disappeared in

a number of patients when their dosage was lowered and alcohol forbidden, most hepatologists were sceptical and spoke of sampling error, although the material included patients with five consecutive biopsies with cirrhosis followed by six or seven consecutive biopsies without cirrhosis. The histology was studied blind. This also has bearing on the discussion of value of liver biopsies in relation to sampling error, which naturally has to be considered.

When we in 1996 re-evaluated the above-mentioned group of 25 patients having had a MTX-induced liver cirrhosis (10), twelve of the patients which we were able to study had normal amino-terminal propeptide of type III procollagen (PIIINP). This is in good accordance with PIIINP being a marker of fibrogenesis and not of fibrosis. We are still happy that this non-invasive marker, which we are very well aware of is not liver specific, but which we believe we and others (11–12) have shown, that as long as serial tests are normal, indicates that no significant development of liver fibrosis is taking place. The simplicity of the test increases its value.

Christensen mentions several more or less elaborate tests for either fibrogenesis or fibrosis. We should like to add, that one of the most recent non-invasive methods studied by the European Liver Fibrosis Group (13) might also be promising for MTX-induced hepatotoxicity in psoriasis. It contains serum levels of nine markers including hyaluronic acid, PIIINP and tissue inhibitors of metalloproteinase-1. The study on 1021 subjects with liver fibrosis detected fibrosis with a sensitivity 90% and absence with negative predictive value 92%.

We agree with Christensen that more investigations are needed to study non-invasive indicators as a whole, while in many situations they may well already replace a liver biopsy. The reduction in observations of MTX-induced liver fibrosis and cirrhosis are multifactorial. We have discussed some. Other reasons would be the far greater choice of drugs available for severe psoriasis together with use of rotational therapy. With rotational therapy the cumulative MTX dosage should be lowered significantly. The alcohol consumption does not seem to have declined among psoriatics from the Nordic countries (14). Discontinuing liver biopsies without using well controlled none invasive methods will with no doubt be followed by a further reduction, however unlikely, with a reduction in morbidity.

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