

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

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In dermatology, methotrexate has been used to treat patients with psoriasis for many years. Despite the emergence of newer, more expensive therapeutic modalities, methotrexate will still have an important role in the management of psoriasis in the future.

A fine review of the use of methotrexate in psoriasis has just been published in the previous issue of this journal by Zachariae (1).

Methotrexate blocks cellular metabolism in several ways. The drug binds to dihydrofolate reductase, and thereby blocks the reduction of folic acid to tetrahydrofolic acid, which is necessary for synthesis of purine and pyrimidine bases. In the cell the drug is transformed to a polyglutamate compound, which inhibits a number of enzymatic processes in nucleic acid metabolism. Methotrexate is most effective in rapidly proliferating cells. In epidermis it blocks the rapid cell turnover, reduces neutrophil and monocyte chemotaxis and decreases the leukotriene-induced intra-

epidermal penetration of granulocytes responsible for the skin lesions seen in psoriasis. In addition to its use in dermatology, methotrexate has proven effective in the management of many oncological and rheumatic diseases, rheumatoid arthritis in particular.

Methotrexate can give rise to many adverse reactions, such as interstitial pneumonitis, pulmonary fibrosis, gastrointestinal side effects including nausea as well as bone marrow suppression. However, its potential for hepatic fibrosis and cirrhosis has for many years been of concern with long-term treatment. The polyglutamated form of methotrexate, which is formed in the metabolism, is retained within the cell long-term. This has been shown to be the major storage form of hepatic methotrexate and may be the metabolite responsible for hepatotoxicity.

Liver toxicity of methotrexate

Concern about hepatotoxicity arose from reports that up to 26% of patients with psoriasis develop cirrhosis on methotrexate therapy. In addition, reports of abnormal histology in up to 51% of pre-treatment liver biopsies, and the suggestion that the pre-treatment abnormalities may increase the risk of further liver injury on methotrexate therapy, have led to intensive monitoring using regular liver biopsies. Initial guidelines for monitoring were formulated by Roenigk et al. in 1972 and were revised later in 1973, 1982, 1988 and 1998 (2). These guidelines recom-

mended baseline liver biopsy at or near the beginning of methotrexate treatment and after each cumulative dose of 1.5 g in order to detect histological abnormalities. Pre-treatment biopsy recommendations were relaxed for the first time in 1998, indicating a baseline biopsy for high-risk individuals only (2). Nevertheless, these strict recommendations for repeated liver biopsies are in marked contrast with clinical experience, which suggests that advanced fibrosis in patients receiving long-term, low-dose, once-weekly oral methotrexate treatment is rare (3). Therefore it seems reasonable to reconsider the use of liver biopsies in these patients.

Risk factors for development of methotrexate-induced liver injury

In psoriasis and rheumatoid arthritis methotrexate is usually administered in a dose of 5 mg up to 20 (25) mg once weekly combined with folic acid supplementation on all other week-days. With this regimen the risk of liver toxicity is small unless risk factors are present (4). These include: 1) reduced renal function of any cause, 2) drugs which decrease the renal elimination, i.e. non-steroid anti-inflammatory drugs, probenecid, sulphonamides, 3) drugs which are highly protein-bound like salicylates and phenytoin, 4) reduced folate stores, 5) advanced age, 6) diabetes mellitus, 7) obesity, 8) hyperlipidemia, 9) pre-existing liver disease, 10) alcoholism and 11) poor compliance. It is highly important to

consider all these factors before methotrexate therapy is started. The dose used should also be based on an evaluation of these factors.

The somewhat higher reported incidence of methotrexate-induced liver toxicity in psoriasis compared to rheumatoid arthritis may well be related to the reportedly higher alcohol consumption among the psoriasis patients. This may also explain the higher prevalence of pre-existing liver disease in patients with psoriasis. Patients may attempt to hide any alcohol problem in order not to be excluded from treatment with methotrexate. The following tests may indicate subclinical alcoholism: elevated gamma glutamyl transferase, elevated middle cell volume (MCV) (in the absence of folic acid or vitamin B12 deficiency) and elevated carbohydrate deficient transferrin (CDT). Elevation of IgA is suggestive of alcoholic liver disease. These tests should be used with a low threshold.

Percutaneous needle biopsy of the liver

In Scandinavia this procedure was first performed in 1939 by Iversen & Roholm (5). For many years a liver biopsy has been considered the gold standard for determination of diagnosis and stage of disease progression, particularly in regard to quantification of fibrosis and diagnosis of cirrhosis. A needle diameter of no less than 1.6 mm is considered necessary for sufficient liver tissue to

be obtained for a thorough description of the liver structure.

Percutaneous liver biopsy is inconvenient to the patient and may be associated with various side effects. Pain after the procedure is rather common (up to 30%). Intrahepatic haematomas can be detected by ultrasound in about 25% of the patients one day after the biopsy, but are usually harmless. Other side effects include intraperitoneal or intrathoracic bleeding, haemobilia and more rarely biliary peritonitis or even death (in about 0.1%) (6).

Sampling variation in liver biopsies is marked

The findings in a liver biopsy including the amount of fibrosis are dependent on the particular sample obtained. Using surgical samples of livers from patients with chronic hepatitis C, measurement of fibrosis has been performed on virtual biopsy specimens of increasing length obtained from a digitized image of the whole biopsy section. The coefficient of variation of fibrosis measurement with 15 mm long biopsy specimens was 55% and for biopsy specimens of 25 mm length it was 45%. The coefficient of variation did not decrease further with even longer biopsies (7). Thus, sampling variability of fibrosis is a significant limitation in the assessment of fibrosis with liver biopsy.

In addition, diffuse parenchymal liver diseases like steatosis, viral

hepatitis, fibrosis, cirrhosis and drug induced liver diseases may not involve the whole liver homogeneously. Thus the findings in simultaneous laparoscopic biopsies from the right and left lobes of the liver may be markedly different even when sampled under direct observation and read by the same experienced pathologist (8). This means that in diffuse parenchymal liver diseases a liver biopsy cannot be considered representative of the whole liver.

Assessment of histologic abnormality - especially fibrosis

The possible abnormalities include portal tract inflammation, steatosis, Kupffer cell proliferation, Ito cell enlargement, increased collagen in the space of Disse, portal fibrosis and eventually cirrhosis. Of these changes the amount of fibrosis is the most important. After the original classification by Roenigk et al. (2) various newer systems have been developed to provide a more detailed semiquantitative classification of liver fibrosis such as the Scheuer score, the Ishak score, the METAVIR score and the Chevalier score. These newer fibrosis scores are much more sensitive than the Roenigk score. Interestingly, using these new scores, hepatic fibrosis has not been found to increase significantly with the cumulative methotrexate dose in patients with psoriasis or rheumatoid arthritis (3, 9).

Cost-benefit of liver biopsy

In patients with rheumatoid arthritis treated with methotrexate it was found in a cost-benefit analysis that a "no biopsy" decision resulted in longer life-expectancy and reduced costs at both 5 and 10 years. The reduction in quality of life due to liver biopsy and related complications was greater than the risk of cirrhosis in those not undergoing biopsy (10). A similar analysis for psoriasis patients, which has not yet been made, should take into account the influence of alcohol, which may confound the results.

Is liver fibrosis dangerous?

Smaller amounts of fibrosis will have little impact on the liver function and on the circulation of blood through the liver. Only if the fibrotic regeneration nodules of liver cirrhosis develop can portal hypertension occur. This in turn can lead to complications like ascites, portosystemic shunting, esophageal varices, variceal bleeding and hepatic encephalopathy. Cirrhosis usually occurs when the pathogenic process operative in the liver has been active for a considerable period of time (many years). However, if the liver cell destruction is more intensive (marked abnormality in aspartate or alanine aminotransferase) cirrhosis may develop more rapidly (in a few years).

Is chronic liver disease reversible?

Most cases of chronic liver disease including alcoholic cirrhosis and chronic viral hepatitis (B and C) have the potential to revert toward a more normal function. Even severe cases of alcoholic cirrhosis with complications like ascites, portal hypertension with esophageal varices or encephalopathy can revert considerably, and after a longer period of many months a near normal liver function can be achieved if the patient abstains permanently from alcohol. Such an improvement may be seen even if cirrhosis is still present in the liver. Nevertheless, the amount of liver connective tissue may also decrease gradually over many years.

Likewise, if hepatitis B or C virus can be successfully eliminated by specific antiviral therapies, the liver tests and the liver function may return to normal after a certain period of time. A similar reversibility is seen in metabolic liver diseases like haemochromatosis or Wilson's disease, if iron or copper can be successfully removed from the body using current therapeutic methods.

In methotrexate toxicity there is also evidence of some reversibility of liver fibrosis after discontinuation of the drug.

Non-invasive methods of assessing liver fibrosis

Over the years, an intensive search for non-invasive fibrosis markers has been made, and a large number of variables and combinations hereof have been evaluated in various liver diseases, in particular in patients with chronic hepatitis C, where the need for non-invasive monitoring is considerable (11). A simple non-invasive fibrosis marker is an AST/ALT-ratio >1 combined with a platelet count $<130 \times 10^9/l$. Another useful marker is the AST to platelet ratio index (APRI). A progressive increase in AST/ALT ratio has been observed in patients with more advanced liver disease as determined by the Child-Pugh and MELD scores, which are used by hepatologists to assess prognosis (12). A decrease in the prothrombin index can also indicate significant liver fibrosis. Direct markers of fibrogenesis like procollagen III N-peptide (PIIINP), laminin, hyaluronan and transforming growth factor- β (TGF- β) can give some information, but these markers are not liver specific.

A more elaborate index like Fibrotest combines the levels of α 2-macroglobulin, α 2-globulin, γ -globulin, apolipoprotein A1, γ GT and bilirubin to a calculated index of fibrosis, which has been tested in more studies. In one of these, discrepant results between biochemical mark-

ers and liver biopsy findings were more likely due to failure of the biopsy (13). The more recent Forn fibrosis index is based on four readily available clinical variables: age, platelet count, gamma glytamyl peptidase and serum cholesterol.

More investigations are needed to fully evaluate the role of these non-invasive fibrosis indicators in the management. However, it is already clear at this stage that in many situations they may well replace a liver biopsy.

Conclusion

Liver biopsy carries a risk of unwanted side effects and provides too little reliable additional information to be routinely recommended at certain cumulative doses of methotrexate. The patients should be monitored using non-invasive methods, including laboratory tests and non-invasive fibrosis scores. The importance of full compliance with the prescribed dosage regimen should be emphasized regularly. The necessity of alcohol abstinence and avoidance of

other potential cofactors for toxicity should be emphasized as well. Patients with constantly or increasingly abnormal liver tests, in particular an increasing non-invasive fibrosis indicator, should be referred to a hepatologist for further evaluation of the risk of continuous methotrexate use. This evaluation may not necessarily include a liver biopsy.

References

1. Zachariae H. Methotrexate for psoriasis in 2004. *Forum Nord Derm Ven* 2004; 9: 98-102.
2. Roenigk HH Jr, Auerbach R, Mailbach H, Weinstein G, Lebwohl M. Methotrexate in psoriasis: Consensus Conference. *J Am Acad Dermatol* 1998; 38: 478-485.
3. Aithal GP, Haugk B, Das S, Card T, Burt AD, Record CO. Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified? *Aliment Pharmacol Ther* 2004; 19: 391-399.
4. Tang H, Neuberger J. Review article: methotrexate in gastroenterology dangerous villain or simply misunderstood? *Aliment Pharmacol Ther* 1996; 10: 851-858.
5. Iversen P, Roholm K. On aspiration biopsy of the liver, with remarks on its diagnostic significance. *Acta Med Scand* 1939; 102: 1
6. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. *Gut* 1999; 45 (Suppl IV) : IV1-IV11.
7. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology*. 2003; 38: 1449-1457.
8. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intra-observer variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002; 97: 2614-2618.
9. Richard S, Guerret S, Gerard F, Tebib JG, Vignon E. Hepatic fibrosis in rheumatoid arthritis treated with methotrexate: application of a new semi-quantitative scoring system. *Rheumatology* 2000; 39: 50-54.
10. Bergquist SR, Felson DT, Prashker MJ, Freedberg KA. The cost-effectiveness of liver biopsy in rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 1995; 38: 326-333.
11. Afdhal NH, Nunes D. Evaluation of liver fibrosis: A concise review. *Am J Gastroenterol* 2004; 99: 1160-1074.
12. Christensen E. Prognostic models including the Child-Pugh, MELD and Mayo risk scores - where are we and where should we go? *J Hepatol* 2004; 41: 344-350.
13. Poynard T, Munteanu M, Imbert-Bismut F, Charlotte F, Thabut D, Le Calvez S, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. *Clin Chem*. 2004; 50: 1344-1355.