Liver histology in patients receiving low dose pulse methotrexate for the treatment of rheumatoid arthritis

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Abstract

The liver histology of 52 patients treated with intermittent low dose pulse methotrexate for rheumatoid arthritis was evaluated using a modification of the Roenigk grading system. Patients studied had had an average of 3·2 years of treatment or had received 1·7 g methotrexate. No patient had cirrhosis; 15 (29%) patients had evidence of mild fibrosis. Histological abnormalities were not predicted by liver function test changes, with the exception that hypoalbuminaemia occurred in 60% of those with grade IV (modified criteria) findings. The need for liver biopsy in patients with rheumatoid arthritis treated with methotrexate before two years or 1500 mg of treatment has not been established. Whether serial liver biopsies will be needed beyond this time has yet to be determined.

Oral low dose pulse methotrexate has been shown in double blind controlled clinical trials to be beneficial in the treatment of rheumatoid arthritis refractory to injectable gold and D-penicillamine.[1–3] Treatment of rheumatoid arthritis with methotrexate is rapidly increasing owing to its efficacy and rapid effect.[4] Methotrexate use in psoriasis showed multiple toxicities and despite administration as a low dose weekly pulse a substantial risk of cirrhosis is present.[5 6] To date liver biopsy has been the only method used to monitor this complication.[7]

Accumulating reports of patients treated with low dose pulse methotrexate for rheumatoid arthritis suggest that the risk of cirrhosis may be less than reported earlier in patients with psoriasis.[8] To validate this impression we evaluated liver histology in 52 patients with rheumatoid arthritis at two medical centres who had been treated with varying doses and duration of low dose pulse methotrexate. Based on analysis of these data, suggestions are offered for hepatic evaluation during methotrexate treatment of rheumatoid arthritis.

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Patients and methods

PATIENTS

Fifty two patients (29 woman, 23 men) treated at rheumatology clinics associated with the Universities of Utah and Washington underwent liver biopsies after signing informed consent. The mean age was 50·8 (26–71) years; mean treatment duration 167 (87–464) weeks; mean cumulative dose 1737 (773–3913) mg. None of the patients had a history of jaundice, one patient had had a prior episode of hepatitis, and another an unexplained ascites in conjunction with a previous illness years before introduction to methotrexate. None of the remaining patients had pre-existing liver disease by history, physical, or pretreatment blood tests. Five patients acknowledged a daily consumption of 60 g of 90 proof liquor a day while the remaining patients claimed to drink 60 g or less of 90 proof liquor a week.

Patients were receiving weekly pulse oral methotrexate treatment of between 7·5 and 15 mg a week given in three divided doses at 12 hour intervals. All patients had received previous treatment with other slow acting antirheumatic drugs: 46 had received gold salts; 42 D-penicillamine; 12 hydroxychloroquine; seven azathioprine; two cyclophosphamide; two chlorambucil; and one chloroquine. Concurrent treatment with other slow acting antirheumatic drugs was not permitted during methotrexate treatment, but non-steroidal anti-inflammatory drugs, aspirin or prednisone, 10 mg or less a day were allowed. Laboratory tests including haemoglobin, leucocyte count, platelet count, differential cell count, alanine transaminase, aspartate transaminase, and serum albumin were done each month. If hepatic enzymes were greater than twice normal on two successive occasions methotrexate treatment was temporarily interrupted until the tests returned to normal. Hypoalbuminaemia was defined as albumin less than the lower limits of normal for that laboratory.

LIVER BIOPSY PROCEDURE

Before percutaneous liver biopsy by the Menghini technique[9] each patient gave a medical history and underwent a physical examination. A complete blood count, leucocyte differential, prothrombin time, partial thromboplastin time, bleeding time, routine blood tests, including aspartate transaminase, alanine transaminase, lactic dehydrogenase, alkaline phosphatase, serum albumin, and urine analysis were performed.

HISTOLOGY

Biopsy specimens were fixed in Bouin fixative and paraffin, and embedded sections were stained with haematoxylin and eosin, Masson's trichrome, and periodic acid-Schiff reagent after diastase digestion. The specimens were independently read and reviewed by two pathologists who were unaware of the patient's condition and duration of treatment. For the purpose of this study the Roenigk system[10] did

not sufficiently distinguish mildly abnormal from normal tissue. Therefore modification of that system[11] was made as follows: grade I=normal; grade II=fatty infiltration or nuclear variation, or both; grade III=inflammation or necrosis, or both; grade IV=fibrosis; and grade V=cirrhosis are equivalent to Roenigk grades III and IV respectively.

STATISTICS

The results were analysed with the Mann-Whitney U test for comparison of two groups and the Kruskal-Wallis test for comparison of more than two groups.

Results

Two independent observers evaluated the liver histology. Nineteen patients had grade II, 16 grade III, 15 grade IV, and none had grade V change. The most common abnormality was variability in nuclear size and staining, which ranged from minimal to marked pleomorphism. Glycogenated nuclei were common. Fatty metamorphosis of both the hepatocytes and sinusoidal lining cells, characterised by fat droplets filling the cytoplasm, was also seen, and some patients had free fat droplets in the portal tracts. Lipogranulomas were also seen and were usually associated with a fine golden brown granular pigment. Kupffer cell hyperplasia was common and often associated with focal necrosis and inflammation. Necrosis and inflammation with lobular disarray was not seen. A mild centrilobular dilatation of the sinusoids was seen in several biopsies. Mild periportal fibrosis was seen but bridging fibrous septa were not. The fibrosis was perisinusoidal and pericellular. Thus although 50 of the 52 biopsy specimens showed some histological changes, only 15 had fibrosis and none had cirrhosis. All of these 15 patients had received non-steroidal anti-inflammatory drugs: 14 had received D-penicillamine and five had been treated with azathioprine. The patient described as having had an illness characterised as unexplained ascites later acknowledged a prior history of alcoholism and had a pretreatment biopsy. The biopsy showed a similar degree of fibrosis to that found after treatment. The patient who had a previous history of hepatitis showed grade II change. The grade of abnormalities did not correlate with age, obesity, duration of treatment, or cumulative dosage of methotrexate.

One or more liver function tests were outside the normal range in 47 of the 52 patients. All of the 15 patients with grade IV (fibrosis) change had either transaminase or alkaline phosphatase abnormalities and nine (60%) of these had hypoalbuminaemia. Of the 22 patients with hypoalbuminaemia, all had histological liver changes and nine (41%) had fibrosis. Forty six of 47 patients with any liver function test abnormality showed hepatic cell change, as did four of the five without liver function test abnormality. Serial increases of the transaminases or alkaline phosphatase were always associated with liver abnormalities and, in 30% of the cases, with fibrosis. Of the 47 patients with abnormal liver tests, 46 had abnormal histopathology. Four of the five with normal tests also had liver changes, however, but none of these had fibrosis.

In summary, serial increases in liver function tests were always associated with some histological change, but only hypoalbuminaemia tended to be characteristic of grade IV changes. Finally in this series, no liver function test was a reliable indicator of the presence or severity of abnormal liver histology.

Discussion

Histological abnormalities varying from mild fatty infiltration to fibrosis were apparent in 50 of 52 liver biopsy specimens obtained from patients with rheumatoid arthritis treated with low dose oral pulse methotrexate for two or more years. Fifteen of the patients had some degree of fibrosis; but none had cirrhosis.

The experience with methotrexate in the treatment of psoriasis raises the possibility that it may be more toxic to liver cells in patients with psoriasis than in those with rheumatoid arthritis.[12 13] Weekly pulse therapy reduces the risk of cirrhosis in patients with psoriasis[14–16]; substantial risk still persists,[15 16] however, and seems to increase rapidly after a cumulative dose of 2–4 g of methotrexate. In one of these studies the prevalence of cirrhosis was 25·6% after five years,[16] though more recent evaluations modify this conclusion.[17] The results of this study and others suggest that cirrhosis is very rare in patients with rheumatoid arthritis even after five years of treatment.[8 14 15 18–20]

For example, Aponte and Petrelli reported that none of the 20 patients who had received 4·7 g methotrexate over 10 or more years had cirrhosis and only two had fibrosis.[8] Weinstein *et al* found fibrosis in six of 17 patients who had received over 900 mg of methotrexate but did not find cirrhosis in any.[19] Hoffmeister reviewed 67 biopsy specimens in 34 patients, 24 of whom had received methotrexate for over three years.[18] None of the patients had cirrhosis, seven had portal fibrosis, and 27 biopsy specimens were normal.

None of the studies, including this one, has shown a correlation of age, duration of treatment, or cumulative dose with incidence or severity of liver disease. This suggests that there may be an underlying susceptibility to fibrosis and may indicate a genetic predisposition to liver disease. A previous study indicated that cirrhosis was more common in patients with the HLA-A1 B8 antigen combination and supports the concept of genetic susceptibility.[21]

The lack of pretreatment biopsies precludes any definitive conclusion about the effect of methotrexate on liver histology in this population. Patients with longstanding rheumatoid arthritis are known to show histological change, probably related to their rheumatoid arthritis.[22] It seems from published studies and our preliminary studies that grade II and III lesions are common in rheumatoid arthritis and that fibrosis is the only lesion unique to methotrexate treatment.[11] If indeed fibrosis is the unique lesion the incidence of methotrexate induced liver disease in this study is 29%.

Previous studies have shown that standard liver chemistries are not predictive pf methotrexate induced liver disease.[7 23] Other non-invasive liver studies, including galactose tolerance tests,[24] liver scans,[25] and fasting bile salt concentration measurements,[26] have been found to be too non-specific and insensitive to be of value in predicting methotrexate induced cirrhosis. Although there are trends in liver test abnormalities, such as hypoalbuminaemia and serial increases of transaminases or alkaline phosphatase, which are more commonly associated with fibrosis on biopsy, standard liver function tests are not indicative of either the presence or severity of liver disease in the patients reported here. Until a more reliable indicator of methotrexate induced liver disease can be identified it is probably premature to alter the recommendation that serial liver biopsies be performed. For rheumatoid arthritis, however, the first biopsy may not be needed until after two years of treatment or a cumulative dose of more than 1500 mg. Whether or not serial liver biopsies will be needed beyond this point has yet to be determined.

In summary, 15/52 (29%) of the patients in this study had evidence of fibrosis, the only lesion apparently unique to methotrexate therapy, after two or more years of low dose pulse methotrexate for the treatment of rheumatoid arthritis. The fibrosis was mild and not associated with cirrhosis. Liver function tests were not predictive of histological abnormalities.

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