Role of Liver Function Tests in Detecting Methotrexate-Induced Liver Damage in Sarcoidosis

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Background: Methotrexate has become a standard second-line agent for the treatment of sarcoidosis. Because sarcoidosis has a high frequency of liver involvement, we routinely perform a liver biopsy after each cumulative gram of methotrexate therapy in patients with sarcoidosis in whom we plan to continue therapy.

Methods: Following a previously described protocol for methotrexate therapy, we have performed 100 liver biopsies on 68 patients with chronic sarcoidosis at our institution. On the basis of the liver biopsy results, we identified the following 4 groups: sarcoidosis (47 cases), toxic effects of methotrexate (14 cases), hepatitis C (2 cases), and normal liver tissue (37 cases).

Results: We found no difference among the groups in terms of age, weight at time of biopsy, the number of patients receiving corticosteroids at the time of biopsy, cumulative dose of methotrexate, race, or sex. The 14 cases of toxic reactions to methotrexate included 5 patients who had undergone 1 or more previous liver biopsies in which the results did not show toxic effects. We found a significant difference between groups for levels of alkaline phosphatase and asparate aminotransferase at the time of starting (or restarting) methotrexate therapy (analysis of variance, \( P < .05 \)). This finding was also true for the liver function tests performed at the time of the biopsy (analysis of variance, \( P < .05 \)). The highest values were for those whose biopsy findings showed sarcoidosis.

Conclusions: Toxic reactions to methotrexate eventually occurred in more than 10% of patients with sarcoidosis treated for more than 2 years with methotrexate. Because of hepatic involvement owing to sarcoidosis, results of serial liver function tests were not useful in determining which patients would have this reaction to methotrexate.

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Methotrexate has been proved to be an effective steroid-sparing agent in some patients with sarcoidosis.\(^1\)\(^2\) The original reports were based on a small number of cases.\(^4\)\(^5\) However, subsequent studies based on larger series have demonstrated that the drug works in 60% to 80% of patients.\(^6\)\(^8\) It has been well tolerated and associated with minimal toxic effects. It has become a standard second-line agent for the treatment of sarcoidosis.\(^8\)

One long-term adverse effect of methotrexate has been hepatotoxicity.\(^10\)\(^11\) In rheumatoid arthritis and psoriasis, guidelines have been established for liver biopsy.\(^12\)\(^14\) For patients with psoriasis, the suggestion is that biopsies be performed after every 1 to 2 g of cumulative methotrexate therapy,\(^14\) because liver function tests were not an effective form of monitoring for methotrexate hepatotoxicity.\(^15\) For rheumatoid arthritis, different recommendations were made.\(^16\) Because the rate of reported irreversible liver damage was low, it was suggested that liver biopsy was not necessary for routine surveillance.\(^17\) In addition, liver function tests, especially measurement of transaminase levels, seemed useful in identifying patients who would need liver biopsies.\(^12\)

Sarcoidosis commonly affects the liver.\(^18\)\(^20\) Liver function abnormalities are seen in more than one third of all patients with sarcoidosis, and liver biopsy results will demonstrate granulomatous disease in more than half of all patients.\(^21\) Results of liver function tests most commonly show an elevated alkaline phosphatase level, but elevated transaminase levels are also seen.

Since we initially reported the usefulness of methotrexate in treating sar-
than 2 years. We herein report the results of the first 100 methotrexate in patients who receive the drug for more treatment using a previously described protocol. The average have received the drug for many years. Our policy is to summarized in approximately every 2 years. The treatment strategy is sum-

lected to determine if the patient could safely continue to re-

he biopsy results were read by 2 experienced hepa-

pathologists (A.K., P.A.B.). A diagnosis of sarcoidosis was made when noncaseating granulomas were identified in the liver tissue. We defined toxic effects of methotrexate using the criteria of Roenigk et al. Grade 1 indicated normal or mild fatty changes, anisocytosis, or mild portal inflammation; grade 2, the addition of severe, spotty hepatocellular necrosis; grade 3A, mild portal fibrosis, with or without fibrotic septa extending into the lobule; grade 3B, piecemeal necrosis or moderate-to-

severe septal fibrosis with portal-to-portal or portal triad–to-

central vein bridging; and grade 4, frank cirrhosis with loss of normal architecture, fibrosis, and nodular regeneration. Patients were believed to have a negative biopsy result if no abnormal changes were identified. In 2 cases, changes consist-
tent with hepatitis C were identified. Both cases were subsequently confirmed by means of recombinant immuno-

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recorded at the time of each biopsy. The initial alkaline phosphatase level was higher in the sarcoidosis and hepatitis C groups than in the other groups. The 2 patients with hepatitis C had higher AST levels than the patients in the other groups. At the time of biopsy, the alkaline phosphatase and transaminase levels were different between the groups. For alkaline phosphatase, the sarcoidosis group had the highest levels (Figure 2). For the transaminases, the 2 patients with hepatitis C had high values (Figure 3). Since only 2 patients had hepatitis C, we also performed between-group comparisons for the sarcoidosis, methotrexate toxicity, and negative groups. The sarcoidosis group had significantly higher levels (ANOVA for alanine aminotransferase, \( P < .001 \); ANOVA for AST, \( P < .01 \)).

To determine the value of serial liver function tests, we evaluated the number of times that the AST level was elevated for the 1 year before biopsy. Figure 4 shows how many patients had 1 or more abnormal AST values among the 9 measurements performed in the previous year. The 2 patients with hepatitis C had multiple elevations of AST levels. The number of elevated AST levels did not differentiate between the methotrexate toxicity and the remaining 2 groups. Eight of 14 patients in the methotrexate toxicity group never had an elevated AST level in the year before the biopsy. The number of times the albumin level was below 3.5 g/dL was small for all 4 groups and did not distinguish between groups (data not shown).

We compared the grade of toxic effects of methotrexate with the liver function test results and the num-
The number of times the AST level was elevated. This finding is summarized in Table 3. The alkaline phosphatase level at the time of the biopsy and the number of times that the AST level was elevated in the year before the biopsy correlated with the severity of the toxic effect, using the Roenigk score. The other variables, including the cumulative dose of methotrexate and the patient’s weight at the time of biopsy, were not related to the severity of toxicity.

Twenty-six patients underwent more than 1 biopsy, and we compared the results of the follow-up biopsy with those of the previous biopsy in 35 instances (patients underwent ≥2 biopsies). Of the 5 cases in which a toxic reaction to methotrexate was detected, 4 of the previous biopsy results had demonstrated sarcoidosis. For the patients without the toxic effects in the follow-up biopsy finding, 21 of 27 had sarcoidosis in their previous biopsy finding.

Methotrexate has become a standard part of therapy for chronic sarcoidosis. Despite its widespread use, little information regarding the effect of methotrexate on the liver is available. To our knowledge, this study represents the largest series of liver biopsy results in methotrexate-treated patients with sarcoidosis.

The need for a liver biopsy to look for a toxic reaction to methotrexate has been the subject of some controversy. The major indications for chronic methotrexate therapy have been psoriasis and rheumatoid arthritis. The guidelines developed by dermatologists suggest performing a liver biopsy after every cumulative 1- to 2-g dose. We chose to use those guidelines for the administration of methotrexate in our patients with sarcoidosis.

An alternative approach has been proposed by the rheumatologists. They have relied on the use of serial liver function tests to identify patients with a toxic reaction to methotrexate. These recommendations are based on the relatively low rate of methotrexate hepatotoxicity seen in patients with rheumatoid arthritis. Careful studies of patients with rheumatoid arthritis found that only patients with persistently elevated transaminase levels or decreased albumin levels had toxic reactions to methotrexate.

For the patients with sarcoidosis, the 14% rate of methotrexate-associated toxic effects was higher than that reported for patients with psoriasis or rheumatoid arthritis. Part of the reason is the underlying liver disease seen in patients with sarcoidosis. In the present study, nearly half of the patients had changes in their liver biopsy results attributed to sarcoidosis that was based on the finding of noncaseating granuloma. The high frequency of sarcoidosis in liver biopsy findings has been noted by others. The associated inflammatory and fibrotic changes seen in the biopsy specimens may overlap with changes seen with toxic reactions to methotrexate. Thus, the limited size of the biopsy specimen could lead us to miss granulomas and overestimate these toxic reactions. All biopsy results of patients with a toxic reaction to methotrexate were reviewed a second time. One case was found to have granulomas and subsequently was reclassified as sarcoidosis. The other possible cause for the increased rate of toxic reactions to methotrexate may be comorbidities leading to an increased risk for methotrexate toxic effects such as corticosteroid use, obesity, and alcohol use. In the present study, we found no difference in weight between the different groups, and the proportions of patients receiving corticosteroids were similar in all 4 groups. Sarcoidosis in the liver may also be a risk factor. However, in the patients who underwent serial liver biopsies, we found no increased risk for development of a toxic reaction to methotrexate if sarcoidosis was seen in the initial biopsy.

In patients with sarcoidosis who had toxic reactions to methotrexate, results of 2 liver function tests correlated with the severity of the reaction. These included the alkaline phosphatase levels at the time of biopsy and the number of times that the AST levels were elevated in the year before the biopsy. These findings are in general agreement with the findings in patients with rheumatoid arthritis treated with methotrexate. Other possible risk factors, such as patient’s weight and the cumulative dose of methotrexate, were not predictive of the degree of the reaction.

In examining all of the abnormal liver function test results obtained during the year before the biopsy, we did not find any pattern predictive of toxic effects. The
patients with sarcoidosis in their liver had higher levels of various liver enzymes. Thus, the predictive value of the liver function tests in the methotrexate toxicity group was lost in the effect of the sarcoidosis on the liver. The absolute liver function test result or the number of abnormal liver values was not clinically useful in determining who should or should not have a liver biopsy. The number of elevated AST values was also not useful in selecting which patients should undergo a liver biopsy. More than half of the patients in the methotrexate toxicity group had no elevated AST levels in the year before biopsy. However, in patients who had toxic reactions to methotrexate, the liver function test results correlated with the severity of liver involvement.

CONCLUSIONS

We performed 100 liver biopsies on patients who were treated with methotrexate for 2 to 8 years. No patient had severe liver disease as a result of methotrexate therapy. However, we identified 14 patients in whom we believed the drug should be discontinued because of a toxic reaction to methotrexate. We found no clinically useful difference between the liver function test results in the methotrexate toxicity and those of the other groups. We believe that liver biopsy remains an important part of screening for toxic reactions to methotrexate in patients with sarcoidosis.

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Table 3. Comparison Between Grade of Toxic Reaction to Methotrexate and Results of Liver Function Tests

<table>
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<tr>
<th>Patient No.</th>
<th>Roenigk Score</th>
<th>Total Methotrexate Dose, g</th>
<th>Dose, g (46-139)</th>
<th>Phosphatase Level, U/L</th>
<th>ALT Level, U/L (7-46)</th>
<th>AST Level, U/L (11-35)</th>
<th>Total Bilirubin Level, mg/dL (0.2-1.0)</th>
<th>Albumin Level, g/dL (3.5-5.0)</th>
<th>Weight, kg</th>
<th>AST Level &gt; 40 U/L</th>
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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.1.
*Explained in Roenigk et al.14
†Correlated with the Roenigk score (r = 0.67; P < .01).
‡Indicates the number of times the value was abnormal among the previous 9 determinations during the year before the biopsy.
§Correlated with the Roenigk score (r = 0.74; P < .01).

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REFERENCES