

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 aspartate 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.¹⁻³ 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.⁹

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-

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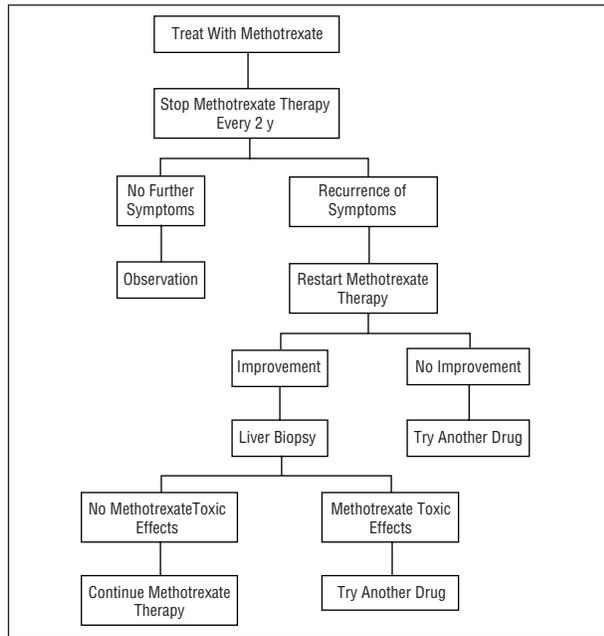


Figure 1. Overall strategy for use of methotrexate at our institution. Patients who improve with methotrexate undergo reevaluation every 2 years. Those patients who relapse when therapy is withdrawn and who improve with methotrexate rechallenge undergo liver biopsy. Adapted from Baughman and Lower.⁸

coidosis at our institution,²² a large number of patients have received the drug for many years.²³ Our policy is to perform a liver biopsy to monitor for toxic effects of methotrexate in patients who receive the drug for more than 2 years.⁸ We herein report the results of the first 100 liver biopsies on these patients.

METHODS

Patients with sarcoidosis who were treated with methotrexate were eligible for evaluation. Patients underwent methotrexate treatment using a previously described protocol.⁶ The average dose of methotrexate was 10 mg/wk. The dosage was adjusted downward if the patient had leukopenia or mucosal toxic effects.

The records of all patients with sarcoidosis who underwent methotrexate treatment at the University of Cincinnati Interstitial Lung Disease and Sarcoidosis Clinic, Cincinnati, Ohio, were recorded in a computer database (Dataease; Sapphire International Ltd, Stratford, Conn). We recorded the amount of methotrexate, and patients underwent evaluation for liver biopsy after each cumulative gram of methotrexate, which was approximately every 2 years. The treatment strategy is summarized in **Figure 1**.⁸ The drug therapy was stopped after each cumulative gram. If the patient's sarcoidosis symptoms recurred (ie, pulmonary, ocular, or dermatologic), the drug therapy was reinstated. If the patient improved, a liver biopsy was performed to determine if the patient could safely continue to receive the drug.

We reviewed patients who underwent liver biopsies at the University of Cincinnati, who represented 90% of the patients followed up in the Interstitial Lung Disease and Sarcoidosis Clinic. Liver biopsies were usually performed via a closed procedure, although some cases included an open liver biopsy as part of another surgical procedure (eg, cholecystectomy). The biopsy tissues were fixed in formalin and embedded in paraffin. We reviewed 3 hematoxylin-eosin-stained slides for each case. Trichrome stain-

ing was also performed to evaluate for fibrosis. Additional special staining was performed as indicated.

Liver function studies were performed initially and at least every 6 weeks while patients were receiving methotrexate. The measurements included levels of alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase, total bilirubin, and albumin. Additional monitoring included renal function tests and complete blood cell counts. Patients with an elevated creatinine level or neutropenia had their dose adjusted, or the drug was withdrawn.⁸ This information was entered into the database at each visit. Other recorded information included the patient's weight and concomitant medicines, including the dose of prednisone.

The biopsy results were read by 2 experienced hepatopathologists (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.¹⁴ Grade 1 indicated normal or mild fatty changes, anisonucleosis, 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 consistent with hepatitis C were identified. Both cases were subsequently confirmed by means of recombinant immunoblot assay.

We performed between-group comparisons using non-parametric analysis, including Kruskal-Wallis analysis of variance (ANOVA). We used the Mann-Whitney test for unpaired data. Correlation was performed using Spearman rank correlation. A *P* value of less than .05 was considered significant.

RESULTS

We reviewed the results of the first 100 liver biopsies performed on a total of 68 patients with sarcoidosis. Thirty-nine patients underwent 1 biopsy; 17, 2 biopsies; and 9, 3 biopsies. The median dosage of methotrexate was 10 mg/wk, with a range of 2.5 to 20 mg. Only 2 patients received 20 mg/wk; the rest received 15 mg/wk or less. The median cumulative dose of methotrexate at the time of biopsy was 1.1 g (range, 1-4 g). All patients had received corticosteroids at one time, and 37 were receiving different dosages of corticosteroids at the time of the biopsy. Of the 68 patients, 16 were men and 52 were women. Self-reported race was white in 14 and African American in 54.

Patients were divided into the following 4 groups based on their biopsy findings: normal, sarcoidosis, methotrexate toxicity, or hepatitis C. **Table 1** summarizes the characteristics of the patients in each of these groups at the time of the biopsy. We found no significant difference between the groups in terms of age, weight, frequency of prednisone therapy, or cumulative dose of methotrexate. Table 1 also includes a breakdown of the race and sex of patients in each group, with no differences between them.

Table 2 summarizes the results of liver function tests as negative, sarcoidosis, methotrexate toxicity, or hepatitis C, at the time of starting or restarting methotrexate therapy (initial). The same measurements were

Table 1. Comparison of Groups on the Basis of Liver Biopsy Results*

	Patient Groups			
	Negative (n = 37)	Sarcoidosis (n = 47)	Methotrexate Toxicity (n = 14)	Hepatitis C (n = 2)
Median age, y (range)	45 (30-67)	47 (21-68)	47 (22-81)	52 (38-62)
No. (%) receiving prednisone at time of biopsy	11 (31)	19 (41)	5 (33)	1 (50)
No. (%) female	22 (59)	35 (74)	11 (79)	2 (100)
No. (%) African American	29 (78)	41 (87)	11 (78)	1 (50)
Median cumulative dose (range) of methotrexate, g	1 (1-4)	1.4 (1-4)	1.2 (1-3)	1.5 (1-2)
Weight at time of biopsy, kg	76.5 (54.0-171.0)	81.9 (58.5-171.0)	85.5 (43.7-189.0)	88.2 (86.4-90.0)

*Groups are explained in the "Methods" section.

Table 2. Liver Function Studies at Baseline and Time of Biopsy*

	Reference Range	Patient Groups, Median (Range)			
		Negative	Sarcoidosis	Methotrexate Toxicity	Hepatitis C
Initial levels					
Alkaline phosphatase, U/L†	46-139	75 (28-220)	89 (55-440)	66 (31-217)	100 (77-123)
AST, U/L‡	11-35	16 (9-122)	27 (9-97)	25 (7-174)	55 (36-74)
Albumin, g/dL	3.5-5.0	4.3 (3.5-4.9)	4.0 (3.5-4.6)	4.0 (2.9-4.6)	4.2 (3.5-4.9)
Levels at time of biopsy					
Alkaline phosphatase, U/L†	46-139	77 (35-154)	107 (55-342)	99 (52-282)	106 (96-116)
ALT, U/L§	7-46	18 (11-51)	27 (11-67)	17 (12-41)	52 (39-65)
AST, U/L§	11-35	17 (8-72)	26 (6-98)	19 (11-48)	60 (53-66)
Total bilirubin, mg/dL	0.2-1.0	0.5 (0.2-1.3)	0.5 (0.1-1.1)	0.5 (0.3-1.1)	1.1 (0.7-1.4)
Albumin, g/dL	3.5-5.0	4.2 (3.2-4.8)	4.2 (3.4-4.9)	4.3 (3.0-4.8)	4.3 (4.0-4.6)

Abbreviations: ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase.
SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.1.

*Groups are explained in the "Methods" section.

† $P < .01$, differences between groups by ANOVA.

‡ $P < .05$, differences between groups by ANOVA.

§ $P < .001$, differences between groups by ANOVA.

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

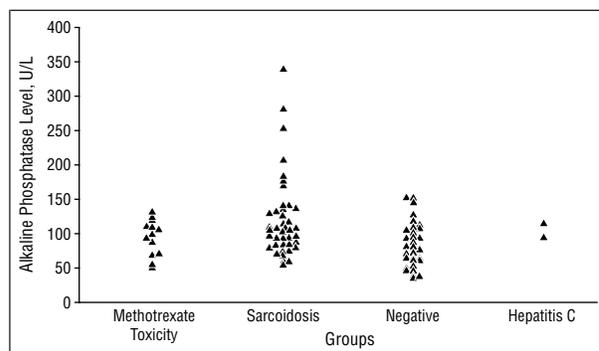


Figure 2. The alkaline phosphatase level at the time of the liver biopsy for all 4 groups is shown. We found a significant difference among the 4 groups (analysis of variance, $P < .01$). Groups are explained in the "Methods" section.

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-

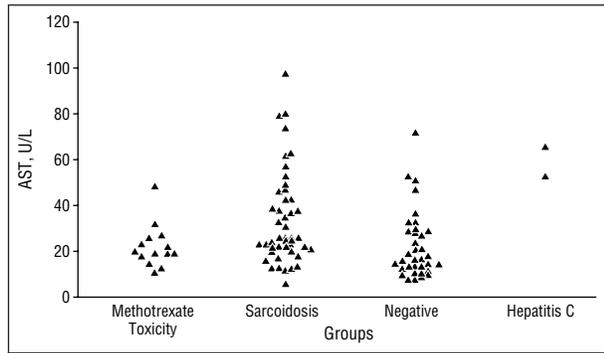


Figure 3. The aspartate aminotransferase (AST) levels at the time of the liver biopsy. We found a significant difference among the 4 groups (analysis of variance [ANOVA], $P < .01$). When we compared the methotrexate toxicity, sarcoidosis, and negative groups only, we still found a significant difference between groups (ANOVA, $P < .01$). However, we found considerable overlap among them. Groups are explained in the "Methods" section.

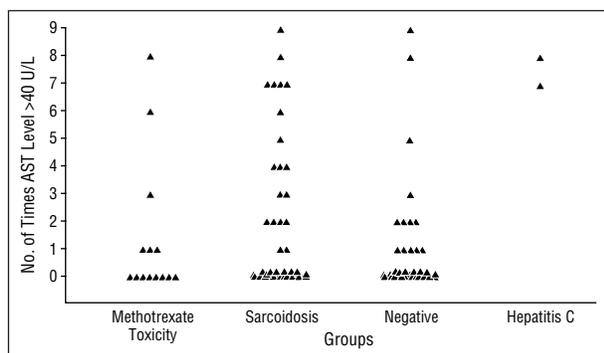


Figure 4. The number of times the aspartate aminotransferase (AST) levels were elevated (>4000 U/L) in the year before the biopsy. We found considerable overlap between the groups. Groups are explained in the "Methods" section.

ber 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.

COMMENT

Methotrexate has become a standard part of therapy for chronic sarcoidosis.^{2,6,8,23-25} Despite its widespread use, little information regarding the effect of methotrexate on the liver is available.⁶ 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.²⁶ 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.¹⁴ We chose to use those guidelines for the administration of methotrexate in our patients with sarcoidosis.⁸

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.¹² These recommendations are based on the relatively low rate of methotrexate hepatotoxicity seen in patients with rheumatoid arthritis.^{27,28} 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.²⁸

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.¹⁸ 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.^{19,21,29} 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.^{12,28} 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

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

Patient No.	Roenigk Score*	Total Methotrexate Dose, g	Liver Function Tests (Reference Range)					Weight, kg	AST Level >40 U/L‡§	Albumin Level <3.5 g/dL‡
			Alkaline Phosphatase Level, U/L† (46-139)	ALT Level, U/L (7-46)	AST Level, U/L (11-35)	Total Bilirubin Level, mg/dL (0.2-1.0)	Albumin Level, g/dL (3.5-5.0)			
1	1	1.0	52	15	15	0.3	4.7	43.7	0	0
2	4	1.5	133	13	22	0.7	3.3	58.1	8	0
3	1	2.5	56	14	11	0.3	3.2	140.4	0	2
4	1	2.2	111	23	23	0.5	3.8	85.5	1	0
5	2	1.0	112	18	19	0.3	4.3	86.0	0	0
6	3A	2.0	107	17	18	0.8	4.3	85.5	0	0
7	2	1.0	69	14	20	0.3	3.9	171.0	1	0
8	2	2.5	71	16	19	0.4	4.8	192.2	0	0
9	2	1.2	99	16	13	0.8	4.4	85.5	0	0
10	2	1.0	125	12	27	0.4	4.5	72.9	3	0
11	3A	1.0	121	28	48	0.3	4.2	71.6	6	0
12	1	3.0	71	22	26	0.5	4.4	102.2	0	0
13	2	1.0	94	24	32	0.6	3.8	97.2	1	0
14	1	1.5	88	17	19	0.6	4.4	150.8	0	0

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 ($r = 0.74$; $P < .01$).

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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