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Methotrexate in sarcoidosis: hematologic and hepatic toxicity encountered in a large cohort over a six year period

Robert P. Baughman[1], Johanna P. Cremers[2], Martina Harmon[1], Elyse E. Lower[1], Marjolein Drent[2,3,4]

[1] University of Cincinnati Medical Center, Cincinnati, OH, USA; [2] ild care foundation research team, Ede, the Netherlands; [3] ILD Center of Excellence, Department of Respiratory Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands; [4] Department of Pharmacology and Toxicology, FHML, University Maastricht, the Netherlands

Abstract. *Background:* Methotrexate (MTX) is a second line agent for treatment of sarcoidosis. Its long term safety and efficacy in sarcoidosis remains unclear. *Methods*: This was a retrospective review of patients seen at the University of Cincinnati Sarcoidosis Clinic over a six year period. For each visit, complete blood count, liver function testing, and dosing and outcome of MTX was noted. For efficacy, we compared the outcome of therapy of a matching subgroup of patients treated with either MTX or infliximab for one year and results scored as improved, stable, or worse based on response of the target organ. *Results:* Over six years, 1606 sarcoidosis patients were seen with a total of 13,576 clinical visits. During the study period, 607 patients (38% of total) were receiving MTX and had available blood work. Moderate elevation of alanine aminotransferase (ALT) (>3 times upper limit normal) was seen in nine (1.6%) patients. White blood count of <1500 cells per cu mm was seen in one patient. At six months, over half of the 44 patients initiated on infliximab and with at least six months of follow-up were better, while only 23% of the 44 of a matched subset of MTX treated patients were better (Chi square=10.566, p=0.0143). At the 12 month assessment, the infliximab treated patients were still more likely to be better than those treated with MTX (Chi square=10.033, p=0.0183). Only 23% of those treated with MTX were worse at twelve months. *Conclusion:* In our study, MTX therapy was associated with very few hepatic or hematologic complications. MTX was less likely than infliximab to improve clinical status. However, only 20% were worse after one year of MTX. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (3): e2020001)*

Key words: sarcoidosis, methtorexate, liver function tests, leukopenia, infliximab

Introduction

Methotrexate (MTX) has been used to treat chronic sarcoidosis for many years (1-3). It has been reported as effective in treating pulmonary,(2;4) ocular,(5) and neurologic disease.(6) In a double blind, placebo controlled trial, it was superior to placebo as a steroid sparing agent.(7) In two surveys, over 90 percent of sarcoidosis specialists considered MTX the drug of choice in patients who had developed intolerance to prednisone.(8;9)

However, a multi-national survey of sarcoidosis specialists revealed that 41% of responding physicians used MTX on five or less of their patients in the previous year, with 10% of the total responders not having used MTX in the past year.(8) For those not using MTX, fear of toxicity was the most commonly cited reason. In addition, some clinicians were unsure of the effectiveness of MTX in treating sarcoidosis.

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Correspondence: Robert P. Baughman MD,
200 Albert Sabin Way, Room 1001,
Cincinnati, OH 45267-0565
E-mail: bob.baughman@uc.edu

The major toxicities of MTX beside gastrointestinal side effects, mainly nausea, are leukopenia and hepatotoxicity (10). Guidelines have been developed to minimize these toxicities in rheumatoid arthritis(11), and similar guidelines have been proposed for sarcoidosis patients.(8) We were interested in the frequency of major hematologic and liver toxicity in our sarcoidosis patients.

There are several agents available to treat advanced sarcoidosis.(12) In addition to MTX, there are other immunosuppressants such as azathioprine,(4) leflunomide,(13;14) and mycophenolate mofetil (15). The tumor necrosis factor (TNF) inhibitors such as infliximab have been reported effective agents for advanced sarcoidosis.(16;17)

The aims of this study were to evaluate the real life safety of MTX in patients with advanced sarcoidosis and to compare the effectiveness of MTX treatment with infliximab.

Methods

We performed a retrospective review of patients seen at the University of Cincinnati Sarcoidosis Clinic over a six year period. Each clinic visit was recorded in a data base (ACCESS, Microsoft) with additional clinical and laboratory information obtained. Patients prescribed MTX alone or in combination with other agents were identified. We also recorded the age, gender, and self-reported race of all patients. Organ involvement was defined using standard criteria.(18) Other data collected included complete blood count, white blood count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, MTX dosage, concurrent prednisone and/or cytotoxic drug use, and presence of known sarcoid liver disease (defined as positive liver biopsy or >3 times upper limit of normal (ULN) liver tests prior to treatment). The protocol has been approved by the University of Cincinnati Institutional Review Board.

Our standard practice is to institute treatment with MTX at an initial dose of 10 mg orally once a week unless the patient's baseline white blood cell count is <4000 cells/cu mm. In leukopenic patients the dose was reduced. Likewise, patients with an elevated serum creatinine would have does adjusted, and those patients with a serum creatinine >2.0 mg would not receive MTX. Complete blood counts along with liver and renal function are assessed every three months while on therapy. For patients whose ALT or AST rose to greater than three times the ULN, the MTX was discontinued. Patients who had MTX discontinued were treated with alternative agents, such as azathioprine. We did not rechallenge patients with MTX.

Toxicity

The study focused on two major side effects of MTX, leukopenia and hepatoxicity. Serial testing including complete blood count (CBCs) and liver function tests (LFTs) were scheduled to be performed every three months. All available testing was recorded at the time and subsequently available for review.

In patients who developed severe leukopenia, defined as a total WBC <1.5*10^3 cells per cu mm, MTX was discontinued. Abnormal liver function testing was defined as an alanine aminotransferase (ALT) >1.5x upper limit of normal (ULN), and an ALT >3x ULN required MTX discontinuation.

Response Assessment

Assessment was performed in those patients who instituted new treatment with a minimum of six months of follow up. To compare the efficacy of MTX to infliximab, a clinical response tool was developed. Known sarcoidosis patients with target organ involvement of lung, skin, eye, or liver were included, and patients were classified according to their response to therapy over the six months after initiation of therapy.

We identified 44 patients who initiated infliximab during the study period and had sufficient follow-up data at six months. We compared these patients to a matched group of MTX treated patients based on age, race, and organ involvement who had also begun therapy during the study period and there was at least six months of follow-up data. None of the MTX group were on infliximab at the time of the analysis of response to therapy. The infliximab patients were on MTX and/or other immunosuppressants including prednisone and azathioprine. However, all patients had progressive disease at the time of starting infliximab.

The clinical response tool captured patient data including drug therapy and dosage at the initial, 6-month, and 12-month interval, affected organs, FVC% predicted, and the evaluator's overall global assessment. For the global assessment, the physician's clinical assessment along with changes in FVC% or steroid-sparing drugs were considered and rated on a Likert scale of 1 to 5 (1=much worse, 2=worse, 3=same, 4=better, 5=much better).

The target organ was that manifestation which was identified as the reason for treatment. Response of the target organ to therapy was determined using predefined criteria for individual organ assessment as well as for the entire patient. Criteria for response are listed below:

Pulmonary

Improvement in the target organ was defined as an increase in at least one of the lung function test parameters by ≥10% of the predicted value or reduction of inflammation in chest imaging (based on official interpretation of chest imaging). Stable was defined as no clinically significant change (increase or reduction ≤10%) in lung function or chest imaging with reduction in steroid dosage. Patients were determined to be worse if there was ≥10% decline in lung function, worsening of chest imaging, or steroid dose could not be tapered. (7, 19, 32)

Ocular

Improvement was considered present when at least one of the inflammatory signs of eye show complete clearance or improvement in one without deterioration in others. Stabilized is defined as all inflammatory signs of eye remain unchanged, and deterioration as an increase in at least one inflammatory sign. Improvement, stabilization, or worsening of disease activity was assessed by the physician based upon increase or decrease in topical steroids such as eye drops, periocular injections given within the past two months and/or patient-reported changes in visual acuity. (7,19;20)

Hepatic

Appropriate laboratory test results were assessed by the physician, especially alkaline phosphatase and bilirubin, before and after therapy. Improvement was defined when elevated tests decreased by 50% of the upper limit of normal. Stabilization included levels which remained unchanged despite reduction in prednisone dosage. Worsened disease included an increase in abnormal LFTs or an increase in prednisone dosage. (14, 16)

Cutaneous

Change from baseline skin lesions were considered improved if lesions were reduced by greater than 50%, stable if there was no clinically significant change, and worse for increase ≥10%. Comparisons of lesions were reported by the same physician. (14, 32)

Assessment of target organ response was based on physician's comments in the patient record. We developed this assessment tool specifically for this study and it was applied to all patients. This assessment was performed by an independent reviewer (MH) who evaluated all patients. This reviewer was not involved in patient care.

Statistics

Results are reported as mean with standard deviations. Comparisons were made between groups using Student t test with a p value of <0.05 being considered significant. Multi regression analysis was performed by incorporating any feature in the model which had a p value of <0.10 on univariate analysis.

Results

Toxicity

During the time period, a total of 1606 sarcoidosis patients were seen with a total of 13,576 clinical visits. Figure 1 demonstrates the number of patients evaluable, including the number who received MTX at any time (869 [54% of total]). During the study period, 607 patients (38% of total) were receiving drugs and had available blood work. These 607 patients constituted the study group. The demographic characteristics and major organ for the group involvement are summarized in Table 1. Granulomatous liver involvement was confirmed by liver biopsy in 48 patients (7.9%); whereas, 11 patients had granulomas identified in their bone marrow.

Table 2 demonstrates the clinical features of those with abnormal liver function test abnormalities

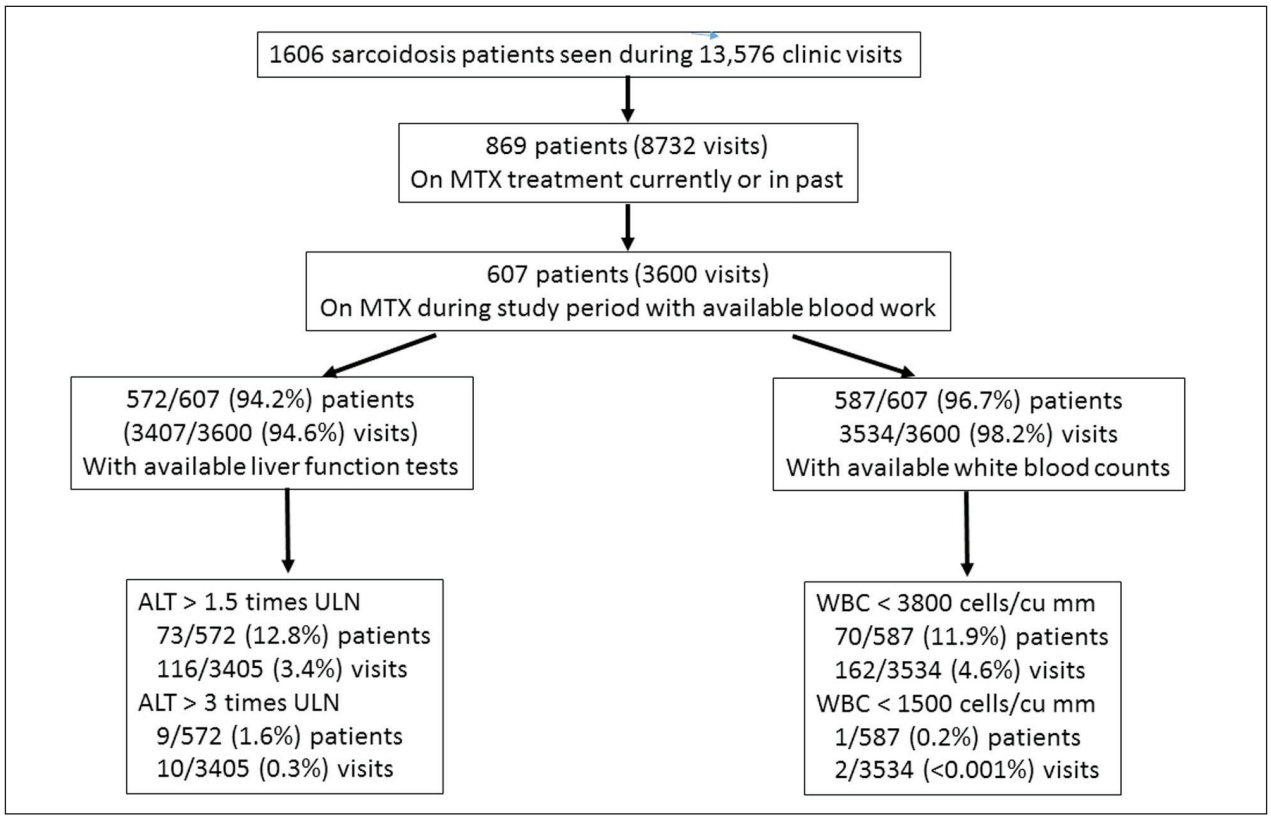

Fig. 1. A flow diagram of all visits seen during the study time period. MTX: methotrexate; ALT: alanine aminotransferase; ULN: upper limit normal; WBC: white blood count

Table 1. Clinical features of the studied methotrexate treated sarcoidosis patients

	Number	Percent of total
Total	607	
Female	446	73.5%
Caucasian *	345	56.8%
Organ		
Lung	491	80.9%
Eyes	264	43.5%
Skin	234	38.6%
CNS	96	15.8%
Liver	48	7.9%
Extra thoracic lymph nodes	67	11.0%
Spleen	30	4.9%
Cardiac	28	4.6%
Sinus	41	6.8%
Bone marrow †	11	1.8%

*Remaining patients are African American except one from India.
†Positive granulomas in bone marrow

(LFTA) versus the remainder of the treated patients. In multiple regression analysis only sex and hepatic sarcoidosis were independent predictors of LFTA. Elevated LFTs were reported within three months of MTX institution in more than half of patients with LFTA. However less 2% of patient had LFTA greater than 3 times upper limit normal and only 1 patient had an ALT or AST greater than 5 times upper limit normal. .

Table 3 depicts the clinical features of those patients with leukopenia versus the remainder of the MTX treated patients. In multiple regression analysis only race but not MTX dose was an independent predictor of leukopenia. None of the patients had infections associated with their leukopenia, including the one patient with a WBC of less than 1500 cells/cu mm.

All nine patients with ALT greater than three times the upper limit of normal had MTX withdrawn and follow-up LFT testing was normal. Patients with leukopenia had their dose of MTX adjusted and follow up testing was stable.

Table 2. Clinical features of the studied sarcoidosis patients with or without liver function abnormalities

	LTA (ALT >1.5 time ULN)	No LTA (ALT<1.5 times ULN)	P value
Total	73 (12.8%)	499 (87%)	
Age, years	48 ± 9.8 *	50 ± 10.8	>0.05
Female §	63 (86%)	324 (72%)	0.010
African American	33 (46%)	219 (44%)	>0.05
Serum creatinine >1.2 mg/dL	3 (4%)	22 (95%)	>0.05
Liver sarcoidosis §	13 (8%)	36 (8%)	0.008
Methotrexate dosage mg/week	9.9 ± 2.6	9.8 ± 3.1	>0.05
Concurrent prednisone	50 (68%)	260 (58%)	>0.05

Table 3. Clinical features of those sarcoidosis patients with or without leukopenia during methotrexate therapy

	Leukopenia (WBC<3800 cells/cu mm)	No leukopenia (WBC>3800 Cells/cu mm)	p-value
Total	70 (11.9%)	517 (88.1%)	
Age, years	50 ±9.5 *	50 ±10.7	>0.05
Female	47 (67%)	387 (75%)	>0.05
African American	39 (56%)	215 (42%)	0.027
Serum creatinine >1.2 mg/dL	4 (5%)	28 (6%)	>0.05
Hepatic sarcoidosis	5 (7%)	47 (9%)	>0.05
Methotrexate dosage mg/week	9.0 ±2.5	9.9 ±2.9	<0.0001
Concurrent prednisone	36 (51%)	307 (60%)	>0.05

Therapy Response

We identified 44 patients who initiated infliximab during the study period and had sufficient follow-up data at six months. We compared these patients to a matched group of MTX treated patients based on age, race, and organ involvement who has also begun therapy during the study period and in whom there was at least six months of follow-up data. The infliximab and MTX groups both con-

tained (28 females and 16 males). There was a similar proportion of lung, skin, eye, or liver involvement in the two groups.

Patient response to either therapy was calculated after six months and twelve months of treatment and summarized in Table 4. Only 10 (23%) of patients who started with MTX were worse by one year of therapy. No patient was much worse after either treatment and we did not include that response in our subsequent Chi square analysis. While there was an increase in the number of patients who were stable or better after 12 versus six months of MTX therapy, the differences in response were not significant (Chi square=3.294, p>0.05%). There was no significant difference in the response rate after 6 versus 12 monhts of infliximab.

Figure 2 summarizes the response rate for the MTX versus infliximab treated patients. Sarcoidosis patients treated with infliximab experienced a more favorable response to therapy compared to MTX treated patients at both six and 12 months. At six months, over half of the patients treated with infliximab were better or much better, while only 21% of the MTX treated patients were better and around a third of the MTX treated patients were worse. The response rate was significantly different between these two regimens (Chi square=11.804, p=0.0081). At the 12 month assessment, the infliximab treated patients were still more likely to be better than those treated with MTX. On the other hand, the percent of patients who worsened with MTX decreased from 36% at 6 months to 21% at 12 months. Again the rates of response significantly differed between MTX and infliximab (Chi square=11.141, p=0.011). The majority of patients in both groups were either stable or better at both the six and 12 months timepoints. Patients treated with infliximab had a more favorable response to therapy compared to MTX at both six and 12 months.

Discussion

We identified more than 600 sarcoidosis patients treated with MTX at our institution over a six year period. Leukopenia and elevated liver transaminases were identified in about ten percent of cases. Severe leukopenia was found in only one patient. Elevation of transaminases to greater than three times upper limit normal was seen in only nine patients. MTX was effective in treating the majority of these sarcoidosis patients. We did not encounter any other adverse events leading to discontinuation of MTX during this time period. This may in part to our dosage of methotrexate. The initial dose of MTX used at our center was 10 mg once a week. This dose was developed by our group as part of our initial reports on using methotrexate in sarcoidosis (2;21). This dose was used in the only double blind, placebo controlled trial of methotrexate for sarcoidosis (7).

MTX has been reported as a steroid sparing agent in sarcoidosis for many years (1;22). However, these early studies evaluated short courses of treatment and dosing based on experience in malignancy and rheumatoid arthritis. We started prospectively using MTX in sarcoidosis patients with two major

Table 4. Patient outcomes in infliximab versus methotrexate treatment

	1=Much Worse	2=Worse	3=Same	4=Better	5=Much Better	Chi	p-value
6 Months infliximab	0	7	13	19	5	11.804	0.008
6 months methotrexate	0	17	20	9	1		
12 months infliximab	0	5	14	15	5	11.141	0.011
12 months methotrexate	0	10	27	10	0		

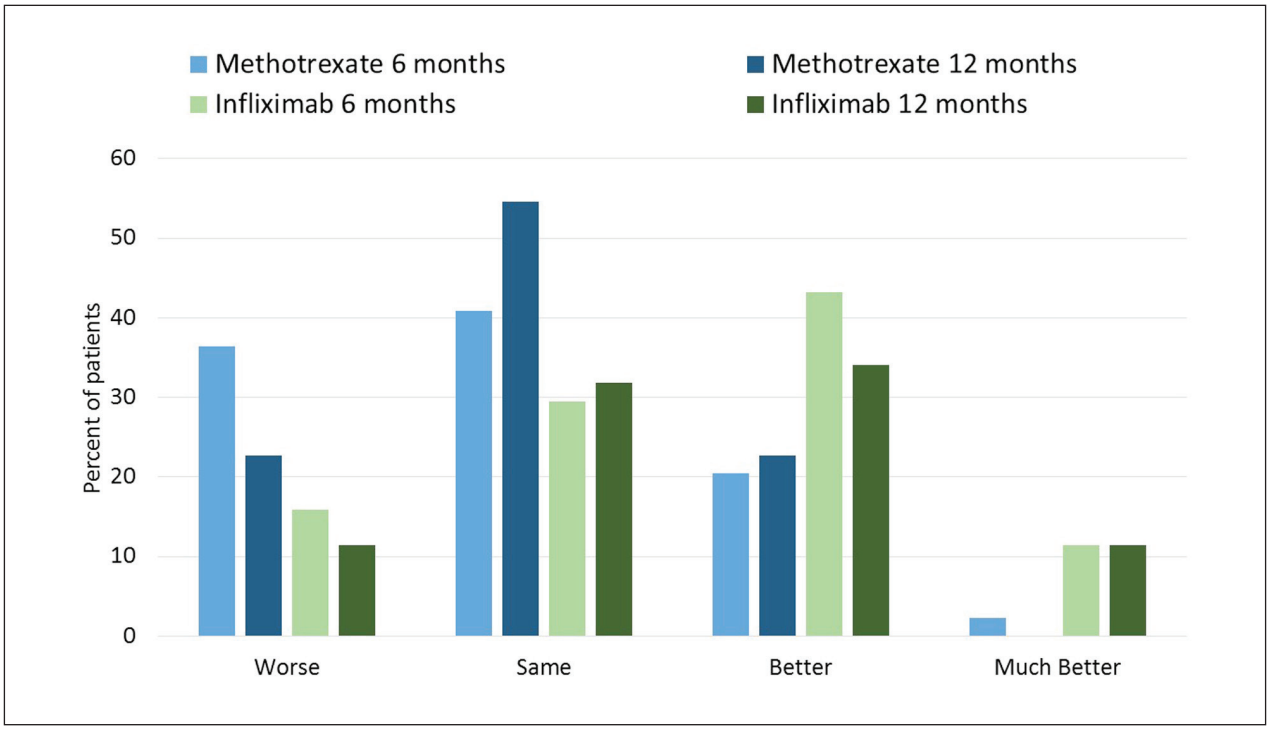

Fig. 2. Response rate for methotrexate at 6 months (light blue) and 12 months (dark blue) versus infliximab at 6 months (light green) and 12 months (dark gree). The response rate was significantly different between these two regimens (Chi square=11.804, p=0.0081). See text for details regarding level of response.

modifications from the early literature. We chose to use a lower dose, since we had demonstrated sarcoidosis patients often have hematologic abnormalities due to bone marrow suppression from the disease (23;24). We also noted that it could take six months or longer to achieve objective disease improvement with MTX treatment (2). Furthermore, we have reported that prolonged use of MTX is associated with good clinical response with limited toxicity (21). Others have demonstrated that MTX is effective in sarcoidosis and less toxic than other agents such as azathioprine (4;25).

The initial dose of MTX we used in this study was 10 mg once a week. This is consistent with our prior studies and within published guidelines for treating sarcoidosis (8) and reported by others (3). Others have used initially 10 mg, but would titrate up to 15 mg a week based on blood monitoring (4). It is unclear that higher doses are more effective and they may just be more toxic. The routine use of 10 mg a week or lower was based on observation of the low toxicity seen in our original series (2;21). This report found a similar very low rate of hepatic and hematologic toxicity. In rheumatoid arthritis, it has been found that higher doses of methotrexate are associated with a better clinical response but more toxicity (26). In a retrospective observational study of sarcoidosis patients, the dose of MTX varied based on treating physician preference. There was no difference in response rate between 10, 12.5, or 15 mg a week (3).

While some physicians feel MTX should be considered as first choice for steroid sparing in sarcoidosis (9;27), a poll of sarcoidosis experts revealed a significant proportion rarely if ever used MTX (8). This paradox seemed be due multiple factors including concern about drug toxicity, poor understanding of MTX efficacy as a steroid sparing agent, misperception of low dose steroid toxicity, and lack of experience with the agent. While there is little one can do about lack of experience except encourage use of drug, we felt that better defining the risk and effectiveness of MTX in sarcoidosis could enhance the usage of this steroid sparing agent.

Based on expert opinion, guidelines have been established regarding the frequency of performing CBC and LFTs (8). In those guidelines, a range frequency employed various centers was reported. Based on these reports the guideline say, "When starting MTX or increasing the dose, ALT with or without AST, creatinine and CBC should be monitored every 3–6 weeks until a stable dose is reached, and every 1–3 months thereafter; after stabilization the monitoring interval can be extended to every 6 months". This statement was not supported by any clinical studies, which was acknowledged in the guideline report (8). In the current study, we report the outcome of monitoring patients every three months as long as they are on therapy. Our results demonstrate that every three month monitoring was a safe method of evaluating patients when using the doses we prescribe.

MTX suppresses the bone marrow and at high doses can cause pancytopenia. In our practice, we use low doses of MTX to avoid such toxicity, and more important, in our experience this lower dose is effective. As seen in Figure 1, our protocol avoids significant leukopenia in the vast majority of patients. This study would suggest that such a guideline would identify the rare patient who develops leukopenia and that severe leukopenia may then be avoided. For patients with leukopenia, the MTX dosage was lower (Table 3). During the study period, the dose of MTX was adjusted based on WBC and MTX was not an independent predictor of leukopenia.

MTX can be hepatotoxic (28). Unlike leukopenia, the rate of liver damage from MTX does not seem to be dose dependent (29). It has been suggested that cumulative dose may be associated with increased risk of hepatotoxicity (30), however not all studies found such an association (10;31), including a study in sarcoidosis (32). This study was not able to detect an impact for cumulative dose, in part because of the small number of cases with significant liver function test abnormalities. We feel that continued liver function testing is warranted in these patients, even with prolonged therapy.

Liver biopsy is the most definitive way to identify MTX hepatotoxicity. We previously reported on the role of liver biopsy in detecting MTX hepatotoxicity (32). However, that procedure has been mostly replaced by liver function testing and recommendations based on the results of serial testing. In rheumatoid arthritis, it has been proposed that a serum transaminase of greater than three times the upper limit of normal be considered abnormal (33). This has been adapted for sarcoidosis patients (8). In sarcoidosis, one has to consider that liver involvement from the underlying disease may cause elevated transaminases (32). The current study rarely identified increased transaminases on serial testing. When it was encountered, our practice was to switch to azathioprine or mycophenolate, since these agents have reported lower rates of hepatotoxicity (12). Others have found that the changes in liver testing may reverse with reducing the dose of MTX. MTX was often used in conjunction with the anti-TNF agents infliximab and adalimumab. This has been recommended to reduce allergic reactions to infliximab and may increase effectiveness of the anti-TNF agents (34;35).

Several potential drugs, including MTX and infliximab, have been shown effective in patients who have worsening disease despite treatment with prednisone and cytotoxic agents (17;36). These studies focused on response of the lung, usually assessed by changes in forced vital capacity. Our study confirmed that infliximab was effective in the majority of patients able to take at least six months of therapy. In order to capture the benefit of therapy in various sarcoidosis phenotypes, we used a novel instrument which assessed individual organs affected and incorporated the physician global assessment. The use of physician global assessment and scoring individual organ response have been reported previously (17;37). While our system was not prospectively captured, it was easily adapted to information readily available in the patient's chart. The instrument was developed to evaluate response rates of different target organs. In our study, the number of patients with specific organ involvement such as brain or heart was insufficient to provide comparison of response rate.

We subsequently used this instrument to assess patient outcomes in infliximab treated patients versus a subset of the MTX treated patients. The MTX treated patients were matched to the infliximab treated patients to compare response rates. We chose this comparison because previous data had suggested infliximab was more potent that MTX in sarcoidosis. In line with another study, the onset of action and efficacy was less robust with MTX compared to infliximab (2). However, after one year, only 21% of

patients felt worse while receiving MTX. This is in line with other studies evaluating MTX response in sarcoidosis (3;21). However, decisions about treatment need to incorporate expected outcomes along with cost, drug availability, and possible long term toxicities which were not assessed in this study. For this comparison, we chose MTX treated patients who had not received infliximab or other third line treatments during the time of analysis. On the other hand, the infliximab patients had been receiving MTX, prednisone, and/or other antimetabolites at time of initiating infliximab. Infliximab is a third line agent that is usually added when patients have continued progression on first and second line immunosuppressants (27). The response rate to infliximab was the effect of addition of that drug to baseline treatment.

There are several limitations to this retrospective study. We focused on hematologic and hepatotoxicity. Other complications such as mucositis, nausea, and infection were not analyzed. While no patient discontinued drug for those reasons, minor dose modifications may have occurred as a result of these complications. Although there were no established criteria for changing drug therapy, only two health care providers (RPB and EEL) evaluated and prescribed treatment. Since sarcoidosis is a multi-organ disease, response in one organ may not mean a similar response in another organ. The study focused on the clinically important target organ for which the patient was undergoing therapy. This instrument was able to detect a significant difference in the two treatment modalities for the whole patient population. Given the relative small number of patients treated with infliximab, we did not perform analysis on specific manifestations of sarcoidosis. We also chose to compare MTX to infliximab. We did not analyze the rate of response of other anti-metabolites such as azathioprine. Infliximab treated patients had usually progressed despite treatment with MTX or similar second line agents (27). Therefore, the MTX patients were probably less severe. However the fact that patients had a better response rate to infliximab enforces the perception that anti-TNF agents are more potent in sarcoidosis. The dose of prednisone was not kept the same through the study. This the response to MTX and infliximab may have been skewed by concomitant glucocorticoid use. During the time of this study, many patients were withdrawn from infliximab because of insurance and/or infections. This is a less common problem now, but we still see that a quarter of patients on infliximab have drug discontinued for these reasons (38). We did not further analyze those patients who received less than one year of treatment and this may bias the response rate we reported with infliximab.

We conclude that MTX was a safe and effective treatment for sarcoidosis patients. The proposed monitoring of sarcoidosis patients treated with MTX (8) was effective in detecting liver and hematologic abnormalities.

References

1. Israel HL. The treatment of sarcoidosis. Postgrad Med J 1970; 46:537-540.
2. Lower EE, Baughman RP. The use of low dose methotrexate in refractory sarcoidosis. Am J Med Sci 1990; 299:153-157.
3. Fang C, Zhang Q, Wang N, Jung X, Xu Z. Effectiveness and tolerability of methotrexate in pulmonary sarcoidosis: a single center real-world study. Sarcoidosis Vasc Diffuse Lung Dis 2019; 36(3):217-227.
4. Vorselaars AD, Wuyts WA, Vorselaars VM, Zanen P, Deneer VH, Veltkamp M et al. Methotrexate versus azathioprine in second line therapy of sarcoidosis. Chest 2013; 144:805-812.
5. Baughman RP, Lower EE, Ingledue R, Kaufman AH. Management of ocular sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2012; 29:26-33.
6. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurologic sarcoidosis. Arch Intern Med 1997; 157:1864-1868.
7. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. Sarcoidosis Vasc Diffuse Lung Dis 2000; 17:60-66.
8. Cremers JP, Drent M, Bast A, Shigemitsu H, Baughman RP, Valeyre D et al. Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: integrating systematic literature research and expert opinion of sarcoidologists worldwide. Curr Opin Pulm Med 2013; 19:545-561.
9. Schutt AC, Bullington WM, Judson MA. Pharmacotherapy for pulmonary sarcoidosis: a Delphi consensus study. Respir Med 2010; 104(5):717-723.
10. Dubey L, Chatterjee S, Ghosh A. Hepatic and hematological adverse effects of long-term low-dose methotrexate therapy in rheumatoid arthritis: An observational study. Indian J Pharmacol 2016; 48(5):591-594.
11. Pavy S, Constantin A, Pham T, Gossec L, Maillefert JF, Cantagrel A et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. Joint Bone Spine 2006; 73(4):388-395.
12. James WE, Baughman R. Treatment of sarcoidosis: grading the evidence. Expert Rev Clin Pharmacol 2018;1-11.
13. Sahoo DH, Bandyopadhyay D, Xu M, Pearson K, Parambil JG, Lazar CA et al. Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. Eur Respir J 2011; 38:1145-1150.
14. Baughman RP, Lower EE. Leflunomide for chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2004; 21:43-48.
15. Hamzeh N, Voelker A, Forssen A, Gottschall EB, Rose C, Mroz P

et al. Efficacy of mycophenolate mofetil in sarcoidosis. Respir Med 2014; 108:1663-1669.
16. Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, Maucort-Boulch D, Marquet A, Perard L et al. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. Semin Arthritis Rheum 2017; 47(2):288-294.
17. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, Du BR et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 2006; 174(7):795-802.
18. Judson MA, Baughman RP, Teirstein AS, Terrin ML, Yeager HJr, the ACCESS Research group. Defining organ involvement in sarcoidosis: the ACCESS proposed instrument. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16:75-86.
19. Erckens RJ, Mostard RL, Wijnen PA, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. Graefes Arch Clin Exp Ophthalmol 2012; 250:713-720.
20. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest 2005; 128(2):1062-1067.
21. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. Arch Intern Med 1995; 155:846-851.
22. Lacher MJ. Spontaneous remission response to methotrexate in sarcoidosis. Ann Intern Med 1968; 69:1247-1248.
23. Lower EE, Smith JT, Martelo OJ, Baughman RP. The anemia of sarcoidosis. Sarcoidosis 1988; 5:51-55.
24. Browne PM, Sharma OP, Salkin D. Bone marrow sarcoidosis. JAMA 1978; 240:43-50.
25. Vucinic VM. What is the future of methotrexate in sarcoidosis? A study and review. Curr Opin Pulm Med 2002; 8(5):470-476.
26. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2009; 68(7):1094-1099.
27. Rahaghi FF, Baughman RP, Saketkoo LA, Sweiss NJ, Barney JB, Birring SS et al. Delphi consensus recommendations for a treatment algorithm in pulmonary sarcoidosis. Eur Resp Rev 2020;in press.
28. Schnabel A, Gross WL. Low-dose methotrexate in rheumatic diseases--efficacy, side effects, and risk factors for side effects. Semin Arthritis Rheum 1994; 23(5):310-327.
29. Fathi NH, Mitros F, Hoffman J, Straniero N, Labreque D, Koehnke R et al. Longitudinal measurement of methotrexate liver concentrations does not correlate with liver damage, clinical efficacy, or toxicity during a 3.5 year double blind study in rheumatoid arthritis. J Rheumatol 2002; 29(10):2092-2098.
30. Kevat S, Ahern M, Hall P. Hepatotoxicity of methotrexate in rheumatic diseases. Med Toxicol Adverse Drug Exp 1988; 3(3):197-208.
31. Hashkes PJ, Balistreri WF, Bove KE, Ballard ET, Passo MH. The relationship of hepatotoxic risk factors and liver histology in methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr 1999; 134(1):47-52.
32. Baughman RP, Koehler A, Bejarano PA, Lower EE, Weber FL, Jr. Role of liver function tests in detecting methotrexate-induced liver damage in sarcoidosis. Arch Intern Med 2003; 163(5):615-620.
33. Kremer JM, Alarcon GS, Lightfoot RW, Jr., Willkens RF, Furst DE, Williams et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994; 37(3):316-328.
34. Drent M, Cremers JP, Jansen TL, Baughman RP. Practical eminence and experience-based recommendations for use of TNF-alpha inhibitors in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31(2):91-107.
35. Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, Rispens T et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. Ann Rheum Dis 2015; 74(3):513-518.
36. Crommelin HA, Vorselaars AD, Van Moorsel CH, Korenromp IH, Deneer VH, Grutters JC. Anti-TNF therapeutics for the treatment of sarcoidosis. Immunotherapy 2014; 6(10):1127-1143.
37. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. Eur Respir J 2008; 31(6):1189-1196.
38. Lower EE, Sturdivant M, Grate L, Baughman RP. Use of third-line therapies in advanced sarcoidosis. Clin Exp Rheumatol 2019;14410.