

Novel Therapies for Sarcoidosis

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ABSTRACT

The treatment of sarcoidosis remains controversial. Corticosteroids remain the cornerstone of therapy, but immunosuppressive, cytotoxic, and immunomodulatory agents have emerged as viable therapeutic options for patients failing or experiencing adverse effects from corticosteroids. Published data are most extensive with methotrexate, but favorable responses have been noted with leflunomide, azathioprine, antimalarial and antimicrobial agents, and tumor necrosis factor- α inhibitors. This review focuses on these novel therapies for sarcoidosis, including indications for use, efficacy, toxicity, and monitoring.

KEYWORDS: Sarcoidosis, immunosuppression, cytotoxic agents, methotrexate, tumor necrosis factor- α , cytokine modulators

The treatment of sarcoidosis has evolved over the past 20 years. Past treatment schedules had focused on the use of corticosteroids and their possible effectiveness in pulmonary disease. However, despite extensive clinical experience, indications for and clinical efficacy of corticosteroids remain controversial.¹ Although it is clear that corticosteroids could be life saving,² many randomized trials failed to demonstrate a clear-cut benefit for corticosteroid therapy.³ A meta-analysis of the studies of corticosteroid therapy supported the use of corticosteroids for pulmonary sarcoidosis.⁴

Over the past 20 years, the use of newer agents has been investigated for sarcoidosis. Many of these drugs were originally evaluated as steroid-sparing agents in rheumatoid arthritis. However, some agents have been useful specifically in sarcoidosis. Table 1 summarizes these drugs. They are placed in three general classes: cytotoxic agents, antimicrobial agents, and cytokine modulators. Examples of drugs in these three classes are listed and will be discussed in detail. There are several other drugs in these categories that either have been used or have been considered for treatment of sarcoidosis.⁵

CYTOTOXIC AGENTS

The use of methotrexate was first described by Lacher in 1968.⁶ The choice of the drug was based on the positive experience using methotrexate for rheumatoid arthritis and psoriasis. Dr. Harold Israel also explored the use of various cytotoxic agents for sarcoidosis.⁷ He also studied chlorambucil,⁸ a drug also reported by Dr. Kataria.⁹ However, these early studies were limited by toxicity of the agents. Problems with these agents included leucopenia and risk for malignancy. For methotrexate, there was a specific concern about hepatic toxicity.

At our institution, we began a multidisciplinary approach evaluating the hematologic status of patients. Patients were followed by a hematologist, hepatologist, and pulmonologist. The dose of the drug was lower than that used for other conditions to minimize the initial risk. We had found that the effect of methotrexate was not apparent for several months. Although patients could have subjective improvement within 2 to 4 months of starting the drug, objective improvement was often not seen until 6 months of therapy.^{10,11}

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Table 1 New Treatments for Sarcoidosis

CYTOTOXIC AGENTS
Methotrexate
Azathioprine
Cyclophosphamide
Leflunomide
ANTIMICROBIAL AGENTS
Chloroquine
Hydroxychloroquine
Minocycline
CYTOKINE MODULATORS
Pentoxifylline
Thalidomide
Infliximab

Methotrexate has proven to be steroid sparing in a double-blind, randomized trial of acute pulmonary sarcoidosis.¹² In our hands, it has proved effective in over 60% of patients treated with the drug for pulmonary,¹³ skin,¹³ ocular,¹⁴ and neurological¹⁵ manifestations. Others have reported a similar response rate for methotrexate in treating sarcoidosis.^{7,16,17} Of the cytotoxic agents, it is the best supported drug for treatment of sarcoidosis.¹⁸

A major concern was bone marrow toxicity of the cytotoxic drugs. In an initial study at our institution, we found leucopenia, lymphopenia, and/or anemia in the majority of patients.¹⁹ Bone marrow involvement in sarcoidosis has been noted by other groups.^{20,21} In a prospective study of newly diagnosed patients with sarcoidosis in the United States, bone marrow involvement was more common in blacks and women.²²

Monitoring white counts has allowed for adjustment of the dose of methotrexate. Most centers now give between 10 to 15 mg once a week of methotrexate, but lower the dose for those who are leukopenic. At our institution, complete blood counts are performed every 2 months and the dose is adjusted accordingly. Table 2 shows the white blood counts and range of weekly doses of methotrexate used for 450 sarcoidosis patients we treated over a 2 year period. The number of patients and number of encounters for each dose are shown. The

white blood counts were lower for those receiving 2.5 mg weekly versus those treated with 10 mg.

Sarcoidosis often affects the liver.²³ Rarely, it can lead to severe liver damage, even cirrhosis.^{24,25} Methotrexate can also affect the liver, even leading to severe cirrhosis.²⁶ Monitoring for hepatotoxicity for patients varies from just routine monitoring of liver function studies²⁷ to routine liver biopsies.²⁸ For sarcoidosis, some centers will monitor liver function tests,¹⁶ whereas others perform routine liver biopsies.²⁹ In a consecutive series of 100 liver biopsies of sarcoidosis patients on chronic methotrexate therapy, 14 patients were felt to have changes consistent with methotrexate toxicity.²⁹ However, 47 patients had changes consistent with sarcoidosis. Routine liver function testing was not useful in distinguishing between these groups. No patient in this series went on to develop irreversible cirrhosis from methotrexate.

Pulmonary toxicity can also be seen with methotrexate.^{30,31} However, fibrotic lung changes due to methotrexate have not been reported in sarcoidosis. In our experience, unexplained cough can be a manifestation of pulmonary toxicity.^{13,32}

Leflunomide, another antimetabolite with properties similar to methotrexate, has been useful in treating rheumatoid arthritis.³³ However, leflunomide has less severe toxicity. In a randomized, double-blind study of 999 rheumatoid arthritis patients, leflunomide was associated with lower liver function test abnormalities.³⁴ Also, five of the 498 patients treated with methotrexate developed interstitial pneumonitis, whereas none of the 501 patients treated with leflunomide developed interstitial pneumonitis.³⁴ Others have successfully used leflunomide in patients with methotrexate-associated pulmonary symptoms.³⁵

Leflunomide has been used to treat sarcoidosis patients.^{35,36} In a series of 32 sarcoidosis patients, the drug was felt to lead to complete response in 16 cases and partial response in nine.³⁵ The drug was used in 17 patients who were intolerant of methotrexate due to either nausea or pulmonary symptoms.

Another aspect of therapy was the use of leflunomide with methotrexate. For 15 patients who had

Table 2 Weekly Dose of Methotrexate for 450 Patients Treated with Methotrexate Alone

Weekly Dose MTX (mg)	White Blood Count Median (Range)		Number of Encounters	Number of Patients ^a
	1000 Cells/mm ³			
2.5	5.2 (2.1–14.1) ^b		87	27
5	6.1 (3.0–15.7)		255	82
7.5	6.4 (3.1–14.4)		180	48
10	7.2 (1.9–21.2)		1101	282
12.5	7.9 (3.6–15.7)		115	32
15	7.3 (3.6–15.4)		305	71

^aPatients could be treated with more than one dose.

^bSignificantly lower than 10 mg weekly dose, $p < .0001$.

progressive sarcoidosis despite at least 6 months of methotrexate, the addition of leflunomide led to complete response in nine cases and partial response in three cases.³⁵ The combination of leflunomide with methotrexate was based on the synergism demonstrated in treating rheumatoid arthritis.³⁷

The future for cytotoxic therapy in sarcoidosis appears to be combinations of treatment.³⁸ In addition to leflunomide, methotrexate has also been combined with azathioprine.^{14,39} The advantage of this combination is the minimization of toxicity while increasing the immunosuppression by multiple mechanism of action. In addition, the combination of a cytotoxic agent with the biological agent infliximab is considered standard.⁴⁰

ANTIMICROBIAL AGENTS

The antimalarial agents have long been known to be effective in treating some forms of sarcoidosis,^{41,42} This has been mostly for skin disease, but others have demonstrated the usefulness of these agents for hypercalcemia,⁴³ chronic pulmonary disease,⁴⁴ and occasionally neurological disease.⁴⁵ These agents do not seem to act as antimicrobial agents, but as anti-inflammatory drugs.

A report demonstrated the utility of minocycline and doxycycline in treating cutaneous sarcoidosis.⁴⁶ This has led to some debate as to the mechanism of action of these drugs. The possibility of an infectious agent as a cause of sarcoidosis has been studied recently.⁴⁷⁻⁴⁹ These antibiotics may have activity against these putative agents, especially *Propionibacterium acnes*. However, these antibiotics have immunosuppressive properties.^{50,51}

CYTOKINE MODULATORS

Tumor necrosis factor- α (TNF- α) has been found to be released by alveolar macrophages from some, but not all,

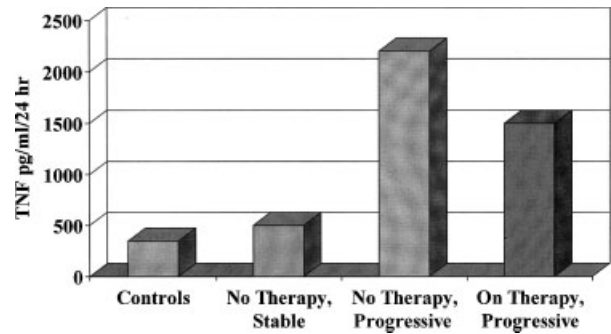


Figure 1 The spontaneous release of tumor necrosis factor- α (TNF- α) by alveolar macrophages (AM) retrieved by bronchoalveolar lavage from four groups of patients: controls, sarcoidosis patients off therapy who were stable, sarcoidosis patients off therapy who worsened over the next 6 months, and sarcoidosis patients on corticosteroid therapy who worsened despite therapy. There was significantly higher release of TNF- α by those patients who progressed. (Adapted from Ziegenhagen et al.⁵⁵)

sarcoidosis patients.⁵²⁻⁵⁴ In one study, Ziegenhagen et al measured TNF- α release from alveolar macrophages from four groups⁵⁵: controls, sarcoidosis patients off therapy who were stable, sarcoidosis patients off therapy who worsened over the next 6 months, and sarcoidosis patients on corticosteroid therapy who worsened despite therapy. As shown in Figure 1, the sarcoidosis patients who worsened over the next 6 months released higher levels of TNF- α . This occurred whether the patients were receiving corticosteroids or not.

These observations have led to the concept of TNF- α as a potential target for therapy in sarcoidosis.⁵⁶ Table 3^{4,13,57-63} lists various agents that have been studied for both their ability to suppress TNF- α release by alveolar macrophages and their treatment of sarcoidosis. These studies support that these drugs, which include corticosteroids and methotrexate, may be successful in treating sarcoidosis by suppressing TNF- α .

Table 3 The Effect of Drugs on Tumor Necrosis Factor- α Release from Alveolar Macrophages and Treatment of Sarcoidosis

Drug	Alveolar Macrophages (AM) Studied	Suppressed TNF- α Release	Effectively Treat Sarcoidosis
Corticosteroids	AM from patients before and after 6 months of therapy	Yes ⁵⁹	Yes ^{4,59}
Methotrexate	AM from patients before and after 6 months of therapy	Yes ⁵⁹	Yes ^{13,59}
Pentoxifylline	AM harvested from patients with sarcoidosis, in vitro testing	Yes ⁶⁰	Yes ⁶¹
Azathioprine	AM from patients before and after 6 months of therapy	Yes ⁶²	Yes ⁶²
Thalidomide	AM harvested from patients with active tuberculosis, in vitro testing	Yes ⁶³	Yes ^{57,58}

Table 4 Biological Anti-Tumor Necrosis Factor- α Agents

Agent	Mechanism of Action	Effectiveness in Psoriatic and Rheumatoid Arthritis	Effectiveness in Crohn's Disease	Effectiveness in Sarcoidosis
Etanercept	Soluble TNF- α receptor antagonist	Yes ^{70,71}	No ⁷²	No ^{65,66}
Infliximab	Chimeric monoclonal anti-TNF- α antibody	Yes ^{40,73}	Yes ^{74,75}	Yes ⁶⁷⁻⁶⁹
Adalimumab	Humanized monoclonal anti-TNF- α antibody	Yes ⁷⁶⁻⁷⁸	Yes ⁷⁹	Yes ⁸⁰⁻⁸²

Not all these agents are equally effective at treating sarcoidosis. Although thalidomide has been found effective in treating chronic cutaneous sarcoidosis,^{57,58} it is not as effective in treating pulmonary disease.⁶⁴ In the latter study, the use of thalidomide may have been limited by the toxicity of the drug. Somnolence and peripheral neuropathy have been significant problems with higher doses of thalidomide.^{58,64}

Biological agents have been developed that have specific activity against TNF- α . Three of these drugs are available in the United States and are summarized in Table 4.^{40,65–82} These agents all seem to be effective for rheumatoid and psoriatic arthritis. The drugs appear to be quite similar in level of effectiveness. However, there is a marked difference between the effectiveness in the clinical trials of Crohn's disease. In that situation, etanercept is not effective, whereas the two monoclonal antibody agents are both effective.

For sarcoidosis, the majority of the studies have been with etanercept and infliximab. For etanercept, there is limited evidence of effectiveness of the drug for sarcoidosis. In an open-label study of pulmonary sarcoidosis, Utz et al discontinued the study at an early time point because some patients developed progression of their disease.⁶⁵ We studied chronic ocular sarcoidosis who failed methotrexate alone. In a double-blind, randomized trial, etanercept was no better than placebo.⁶⁶ Infliximab was effective in some of these patients who failed etanercept therapy.⁸³

The use of infliximab for sarcoidosis was first reported over 5 years ago.^{67,84} To date, a large number of case reports and case series have been reported.^{68,85,86} These observations led to a recently completed double-blind, placebo-controlled trial of infliximab for sarcoidosis.⁶⁹ This study was the largest randomized trial of any agent for chronic sarcoidosis. All patients were stable but still symptomatic on systemic therapy. The study demonstrated a significant improvement in the forced vital capacity for those treated with infliximab versus those treated with placebo. The overall improvement was 2.5%, but the response to treatment was twice as high for those patients with evidence of more severe disease, such as lower vital capacity, more systemic therapy, or longer duration of disease.

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