SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2012; 29; 26-33

Management of ocular sarcoidosis

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Abstract. *Background:* A step wise approach to the use of cytotoxic and anti-tumor necrosis factor (TNF) antibodies has been developed for managing chronic sarcoidosis. *Objectives:* To provide a summary of our experience with immunosuppressive agents especially methotrexate and the anti-tumor necrosis factor antibodies in treating chronic ocular sarcoidosis. *Study Design and Methods:* This was a retrospective review of 1587 sarcoidosis patients seen at one center over a six year period. All patients with definite or probable ocular sarcoidosis were identified. *Results:* A total of 465 (29%) of the sarcoidosis patients experienced ocular disease. Of these, 365 patients were treated with methotrexate (MTX) for their eye disease with 281 (77% of those started on MTX) still receiving MTX at the end of the study. Methotrexate was the only systemic therapy prescribed in 115 patients while 101 patients also received concurrent prednisone. Other combinations administered include MTX plus azathioprine and/or leflunomide. A total of 25 patients were treated with the monoclonal anti-TNF antibodies infliximab (19 patients) or adalimumab (6 patients). While all patients initially responded to anti-TNF therapy, only ten patients experienced a sustained response with ongoing therapy or complete remission of ocular disease. Recurrent infections, adverse drug events, or financial constraints were responsible for most drug discontinuations. *Conclusion*: Most cases of chronic ocular sarcoidosis respond well to immunosuppressive therapy. However, patients may require combination therapy to achieve and maintain disease control. The use of anti-TNF agents for refractory disease is encouraging but can be accompanied by significant toxicity. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 26-33)*

Key words:

Introduction

Ocular involvement has been reported in 25-40% of United States sarcoidosis patients (1, 2). This target organ, which more commonly affects African Americans than Caucasians (3), can encompass several manifestations with uveitis the most common affliction (4).

Several therapies have been proposed for the treatment of ocular disease. For anterior uveitis, topical corticosteroids may be adequate (4). However, patients with chronic uveitis, especially those with involvement of the intermediate or posterior chambers, systemic therapy is frequently required. For many years, cytotoxic therapy has been prescribed with MTX the most commonly reported agent (5-8). However, refractory cases of ocular sarcoidosis may respond to infliximab (9, 10).

Our clinic has used a variety of corticosteroid sparing agents for the treatment of various manifes-

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tations of sarcoidosis. We review our experience using immunosuppressive therapy for the management of chronic ocular sarcoidosis.

Methods

This was a retrospective review of all sarcoidosis patients seen at the Interstitial Lung Disease and Sarcoidosis Clinic at the University of Cincinnati during a six year period from 2002 to 2008. Patients treated with anti-TNF monoclonal antibodies were followed until May 2011. All patients were diagnosed with sarcoidosis using standard criteria (11) and their records were retrieved from an electronic database (ACCESS, Microsoft, Redmond, WA). Using previously defined criteria, ocular and other organ involvement was categorized as "definite" or "probable" disease (12, 13). The records from each patient visit were reviewed with topical and systemic medications and dosages along with outcomes reported. Only patients with a minimum of six months of follow-up after the first visit were included in the study. The protocol was approved by the University of Cincinnati Medical Center Institutional Review Board. This was a review of existing medical charts and no written consent was obtained for specifically for this study. However, all patients had provided written permission to use information from their medical records for research purposes. Drs. Baughman and Lower have received research grants from Centocor and Celgene for studies of sarcoidosis.

In general, patients were treated using the algorithm shown in Figure 1 (4). Patients initially received local therapy, usually prednisolone acetate ocular drops and in selected cases, periocular corticosteroids. Patients who required topical treatments more than four times a day or repeated periocular corticosteroids were referred for systemic therapy.

A variety of systemic immunosuppressive agents were prescribed including prednisone, methotrexate (MTX), azathioprine (AZA), leflunomide (LEF), and the anti-TNF agents infliximab and adalimumab. The most commonly used initial systemic therapy was MTX. For those patients intolerant or nonresponsive to MTX, alternative agents were selected.

Prednisone was used at an initial dose of 40 mg a day. In some cases of severe disease, patients also received 1000 mg methylprednisolone intravenously daily for three days. Patients receiving prednisone were usually also prescribed a cytotoxic agent such as methotrexate. The dose of prednisone was gradually reduced over time. The usual schedule was to reduce the dose by fifty percent at each visit if the patient was improved or if toxicity was encountered. For patients who were stable for two consecutive visits, the dose was also reduced (14). Not all patients were treated with prednisone. In many cases, topical therapy alone was sufficient to control ocular inflammation and methotrexate or another cytotoxic agent was initiated.

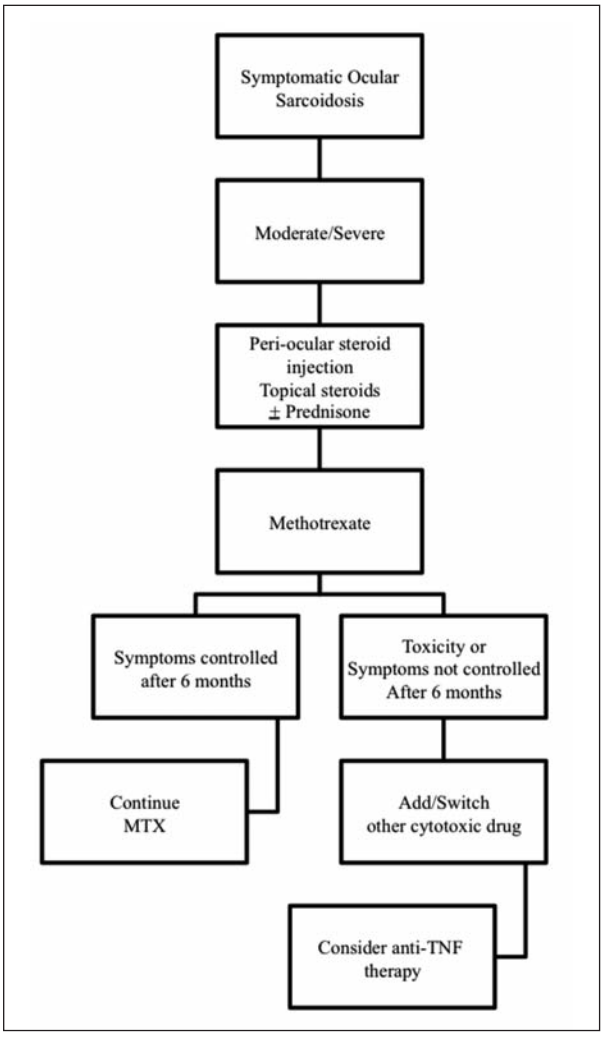

Fig. 1. Algorithm to treatment of ocular sarcoidosis at the University of Cincinnati Interstitial Lung Disease and Sarcoidosis clinic

Methotrexate was prescribed using the previously described regimen for pulmonary sarcoidosis (15). The usual starting dose was 10 mg orally once a week with subsequent dose adjustments based on the white blood count and toxicity such as nausea or mouth sores. Hematologic monitoring, which included completed blood counts along with assessment for liver and renal function, was performed every two to three months. Methotrexate was discontinued in patients who developed unexplained increases in hepatic transaminases on more than two visits. A liver biopsy was performed in some cases to determine whether elevated hepatic transaminases were secondary to sarcoidosis or drug toxicity (16).

Leflunomide (LEF) was administered orally with the usual starting dose of 20 mg once a day. Patients were monitored using the schedule for methotrexate (17). Azathioprine (AZA) was also prescribed using oral doses ranging from 50-150 mg once a day (18). Toxicity monitoring included complete blood count and hepatic function testing every two to three months. For both LEF and AZA, the dose was reduced if nausea or neutropenia developed.

Two monoclonal antibodies directed against tumor necrosis factor (anti-TNF) were prescribed. Infliximab was administered intravenously with initial doses of 3-5 mg/kg initially, 2 weeks later, and then once a month (19). In contrast, adalimumab was subcutaneously injected at a dose of 40 mg every other week. This initial 40 mg dose was increased to weekly in two patients (20).

Statistics: Comparisons were made between groups using either Student's t test or Chi square testing. A p value of less than 0.05 was considered statistically significant.

Results

During the six years of study, 1587 sarcoidosis patients were seen at least once in the Interstitial Lung Disease and Sarcoidosis Clinic at the University of Cincinnati. Of these, 465 (29%) had "definite" or "probable" eye involvement. Table 1 compares the demographic features of those patients with to those without ocular sarcoidosis. In our clinic, patients with ocular disease were significantly younger and more likely to be women and/or African American. Additionally, ocular disease patients were more likely to experience neurologic involvement and less likely to have chest or liver sarcoidosis involvement.

As outlined in Figure 1, patients were treated using a step wise approach, and Table 2 summarizes the systemic therapies prescribed for ocular sarcoidosis patients. Over 95% of patients required some form of systemic therapy for the management of their disease. Initial management often employed topical and systemic corticosteroids. However, several immunosuppressive drugs, including MTX,

Table 1. Demographics of ocular sarcoidosis patients

	Ocular sarcoid		Not ocular darcoid		Chi Square	P Value
Age (mean±S.D.) years	50±11.99		53±11.25			<0.0001
Female	361	77.6%	765	68.2%	13.79	0.0002
Male	104	22.4%	357	31.8%		
Total	465		1122			
Self declared race *						
African American	224	48.2%	441	39.3%	10.78	0.0046
Caucasian	237	51.0%	665	59.3%		
Other ¶	4	0.8%	15	1.3%		
Organ involvement§						
Chest	330	71.0%	984	87.7%	63.46	<0.0001
Skin	163	35.1%	350	31.2%	2.97	NS
Neurologic	85	18.3%	129	11.5%	12.39	0.0004
Liver	24	5.2%	138	12.3%	17.51	<0.0001
Cardiac	10	2.2%	26	2.3%	0	NS

* Also studied two patients from India and one Hispanic Caucasian
¶ Other included India, Jordan, West Indies
§ Patient could have more than one organ involved

Table 2. Systemic treatments of ocular sarcoidosis patients *

Systemic therapy	Any time		Current	
Glucocorticoids	357	76.8%	206	44.3%
Methotrexate	365	78.5%	281	60.4%
Azathioprine	107	23.0%	46	9.9%
Leflunomide	89	19.1%	34	7.3%
Cyclophosphamide	19	4.1%	6	1.3%
Infliximab	19	4.1%	5	1.1%
Adalimumab	6	1.3%	3	0.6%
No therapy	14	3.0%	90	19.4%

* Patients could be on more than one treatment

AZA, and LEF and the anti-TNF drugs were frequently prescribed. Glucocorticosteroids, usually prednisone, were used in 357 (77%) of patients. Rarely were they used exclusively to control ocular disease. In a third of patients treated with prednisone, the drug had been discontinued by the end of the study.

Methotrexate was the most frequently administered agent for our patients. While it was commonly used as a corticosteroid sparing therapy, 102 patients treated with methotrexate never received any prednisone. Figure 2 summarizes the status of those ocular patients treated with MTX at the end of the study period. Table 3 summarizes the racial and gender features of these patiens. There was no significant difference between those treated with methotrexate and the other patients in the study.

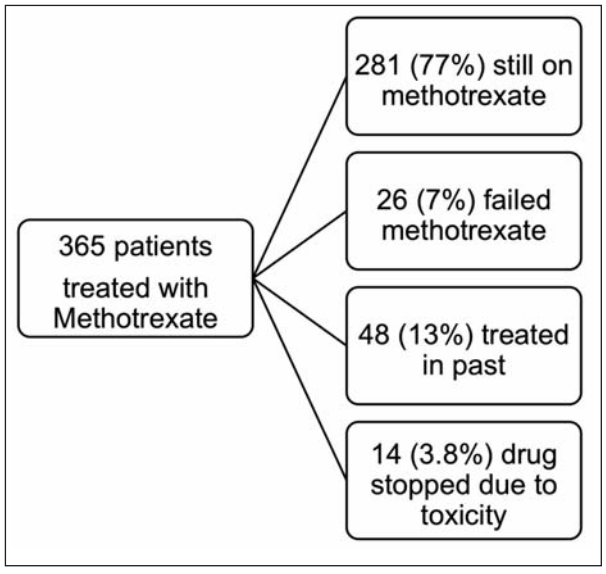

Fig. 2. Status of therapy for the 365 patients with ocular sarcoidosis patients treated with methotrexate

Table 3. Characteristics of patients treated with methotrexate

	Female	Male	Total
African American	142	36	178
Caucasian	146	41	187
Total	188	77	

This drug was both efficacious and well tolerated as 281 (77%) of the 365 MTX treated patients remained on MTX either as a single agent or in combination with other immunosuppressive therapies. The most common reason for MTX discontinuation was disease resolution, which occurred in 13% of cases. An additional 40 patients experienced drug withdrawal either due to toxicity or lack of efficacy. Only 14 of these 40 patients discontinued drug secondary to toxicity, and this represents only 3.8% of the total ocular patients treated with MTX. Liver dysfunction was the most common toxicity with hepatotoxicity confirmed by liver biopsy in six of 12 patients.

For the 281 patients remaining on MTX, more than half were also receiving one or more other immunosuppressive therapies. Table 4 provides specific details regarding the patients who were receiving methotrexate at the end of the study. Included are details regarding patients who had been treated with either azathioprine or leflunomide. Recorded in the table are the cases where those drugs were discontinued due to toxicity. A total of 121 (43% of total) were receiving prednisone at the end of the study. At the end of the study, only 53 (19%) of the MTX treated patients were receiving daily prednisone doses of more than 10 mg.

A total of 25 patients developed refractory disease requiring anti-TNF regimens. Patients could receive multiple therapies, and all but one patient was concurrently treated with a cytotoxic agent: 14 MTX, 10 AZA, and 3 LEF. Table 5 summarizes the outcome of these treatment regimens. At the final evaluation in 2011, only eight patients were still receiving anti-TNF targeted treatment. Of the three patients prescribed adalimumab, two required weekly drug whereas the other patient received dosing every other week. Anti-TNF targeted treatment was discontinued due to disease remission, toxicity, or insurance denial. Only two TNF-treated patients achieved ocular disease remission requiring no further anti-TNF treatment, and both of these patients

Table 4. Patients currently receiving methotrexate

	Patients on no prednisone	Patients on prednisone	All patients	Percent of Total
Total	160	121	281	
Never received prednisone	85			
Past prednisone	75			
Number on >10 prednisone	53		53	18.9%
Additional systemic agents				
Azathioprine				
Current	18	8	26	9.3%
Past	8	5	13	4.6%
Discontinued azathioprine due to toxicity	3	3	6	2.1%
Leflunomide				
Current	16	7	23	8.2%
Past	2	1	3	1.1%
Discontinue due to toxicity	2	1	3	1.1%
Anti-TNF monoclonal antibodies				
Current	6	2	8	2.8%
Discontinue anti-TNF due to toxicity	5	6	11	3.9%

Table 5. Outcome of anti-TNF therapy

	Infliximab	Adalimumab
Number treated	19	6
Ongoing treatment	5 (26%)	3 (50%)
Toxicity leading to discontinuation	8 (42%)	3 (30%)
Insurance causing discontinuation	4 (21%)	0 (0%)
Remission	2 (11%)	
Successful long term therapy (Ongoing Treatment or Remission)	7 (37%)	3 (50%)

required infliximab treatment for more than two years. Post-treatment relapse was frequent with 15 patients experiencing relapse after anti-TNF agent discontinuation. In 11 patients, toxicity necessitated drug withdrawal. Anaphylaxis occurred in two infliximab treated patients; whereas, arthralgias with or without rash developed in seven patients (five received infliximab and two adalimumab). Repeated systemic infections in one infliximab and one adalimumab treated patient lead to therapy stoppage.

Table 6 summarizes the systemic treatment for patients in the study. There was a significant difference in the frequency of current therapy between different agents. Patients were less likely to still be on prednisone or anti-TNF therapy. Toxicity led to discontinuation of cytotoxic and anti-TNF antibody in a significant number of cases. Patients were more likely to have azathioprine or anti-TNF antibodies discontinued due to toxicty than methotrexate ($P<0.0001$ for both). We did not record discontinuation of prednisone due to toxicity, but the goal of therapy was to minimize or discontinue prednisone dosage. By the end of the study, there were still 53 (11%) patients receiving more than 10 mg prednisone.

Discussion

Various eye manifestations in sarcoidosis can run the gamut from minimal symptoms to blindness (21). In this study, we found that thirty percent of our sarcoidosis patients experienced ocular disease for which systemic therapy was frequently required. Although the corticosteroid sparing methotrexate as a single agent or in combination with prednisone

Table 6. Comparison of long term therapy and toxicity of steroid sparing alternatives

	Prednisone	Methotrexate	Azathioprine	Leflunomide	anti-TNF monoclonal antibody
Ever treated	357	365	68	38	25
Current therapy *	205 (57.4%) #	281 (77.0%)	46 (67.6%)	34 (89.5%)	8 (32%)
Discontinue due to toxicity ¶		14 (3.8%)	13 (19.1%) §	3 (7.9%)	11 (44%) †

*Significant difference between groups, Chi square=54.029, p<0.0001
Significantly differs from methotrexate, Chi square=30.510, p<0.0001
¶ Significant difference between groups, Chi square=62.114, p<0.0001
§ Significantly different from methotrexate, Chi square=20.357, p<0.0001
† Significantly different from methotrexate, Chi square=56.397, p<0.0001

was the most commonly prescribed long term treatment, refractory cases often required anti-TNF targeted immunosuppressive therapy which was effective but associated with significant toxicity.

Ocular patients from this single institution retrospective study were usually younger and more likely to be women and/or African American. This increased incidence of ocular disease in African Americans has been reported previously (3, 22). Female predilection has also been previously noted in the US as well as globally (3, 22-24). Young age of onset may reflect the increased incidence of disease in African Americans, who tend to develop ocular disease at a younger age than Caucasians (25). In one large study, when sarcoidosis was diagnosed under the age of forty, women were more likely to have eye disease. In contrast for patients diagnosed after age 40, an increased risk for ocular disease was reported only in African American men (3). This study confirms the previously noted association between neurologic and ocular disease in sarcoidosis patients (26, 27).

Currently there are no evidence based guidelines for the management of ocular sarcoidosis; however, a guideline has been developed for the management of noninfectious uveitis (28). The major emphasis of this guideline was the reduction of systemic glucocorticoids to less than 10 mg per day for prednisone or its equivalent. In our clinic, we have developed a standardized approach to the use of corticosteroid sparing regimen (29) based on our early studies of methotrexate for sarcoidosis (30). At the time of analysis, only 11% of our patients were receving more than 10 mg a day of prednisone. A third of the patients treated with methotrexate never were treated with prednisone.

Methotrexate has been reported beneficial and well tolerated for chronic uveitis (7). It has been reported as a corticosteroid sparing agent in at least two thirds of sarcoidosis patients with ocular sarcoidosis (5-7). In the current study, over 75% of patients treated with MTX remained on methotrexate alone or in combination with low dose prednisone (Table 4). Table 6 summarizes the response rate and frequency of discontinuation due to toxicity for the various systemic agents used in this study. The rate of response and the increased toxicity seen with azathioprine compared to other cytotoxic agents is similar to that reported from a large single institution experience for the treatment of non infectious uveitis (31).

Tumor necrosis factor targeted monoclonal antibodies have been used increasingly for the treatment of a variety of refractory sarcoidosis manifestations (29). Infliximab has been reported efficacious in treating noninfectious chronic uveitis (9, 10, 32, 33), and isolated case reports and small series confirm its benefit in treating sarcoidosis uveitis (9, 10, 34, 35). Adalimumab has also been reported useful in treating ocular inflammation (36). In contrast, the TNF receptor antagonist etanercept was not shown superior to placebo in treating chronic uveitis (37), including sarcoidosis uveitis (38).

In this study, all patients responded to initial anti-TNF therapy; however, many patients required drug withdrawal. In some cases, patients were switched from infliximab to adalimumab because of allergic reactions or insurance company issues. As in other situations, response to adalimumab was noted (39). Allergic infusion reactions to the chimeric monoclonal antibody infliximab can frequently be avoided with the use of the humanized monoclonal anti-TNF antibody adalimumab (40). However, both agents are associated with an increased rate of infections, especially tuberculosis (41). This high rate of relapse after withdrawal of infliximab has

been reported for the treatment of other manifestations of chronic sarcoidosis (42).

In conclusion, we report ocular disease to be a common manifestation of sarcoidosis in our population. This chronic manifestation of sarcoidosis often necessitates prolonged systemic therapy. Methotrexate was an effective and well tolerated corticosteroid sparing agent in these patients. However, refractory ocular disease may require the administration of anti-TNF monoclonal antibodies. These immunosuppressive agents were effective but often associated with toxicity which necessitated drug withdrawal in more than half of the cases.

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