ERS Task Force Therapy for Sarcoidosis

Supplement 1 Individual therapies

The task force made specific recommendations regarding therapy for various manifestations of sarcoidosis. Most of these recommendations involve anti-inflammatory therapies. In general, the dose and duration of therapy is similar for the different manifestations. In those cases where there are differences, these are usually discussed within the individual PICO.

About half of patients with sarcoidosis are treated with one or more anti-inflammatory therapy (1;2). The prolonged dose of these drugs can lead to significant toxicity. Prednisone is the most commonly employed medication for treating sarcoidosis and has been associated with significant morbidity, especially weight gain (3-6). However, other agents may lead to specific toxicity. Table S-1 summarizes the various anti-inflammatory treatments used for sarcoidosis, including their toxicity.

Table S-1

Anti-inflammatory therapies for sarcoidosis

Drug	Dosage	Major Toxicity	Recommended monitoring	Comments
Prednisone/ prednisolone	Initial 20 mg qd Follow up 5-10 mg qd to qod	Diabetes Hypertension Weight gain Osteoporosis Cataracts Glaucoma Moodiness	Bone density Blood pressure and serum glucose	Cumulative toxicity
Methotrexate	10-15 mg once a week	Nausea Leukopenia Hepatotoxicity Pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Leflunomide	10-20 mg qd	Nausea Leukopenia Hepatotoxicity Pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Azathioprine	50-250 mg qd	Nausea Leukopenia Infections Malignancy	CBC	
Mycophenolate	500-1500 mg bid	Diarrhea Leukopenia Infections	CBC	Less experience in sarcoidosis than other agents

		Malignancy		
Infliximab or biosimilars *	3-5 mg/kg initially, 2 weeks later, than once every 4-6 weeks	Infections Allergic reaction	Screen for prior tuberculosis Monitor for allergic reactions Contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active tuberculosis, deep fungal infections	Allergic reactions can be life threatening
Adalimumab *	40 mg every 1-2 weeks	Infections	Screen for prior tuberculosis Monitor for allergic reactions Contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active tuberculosis, deep fungal infections	Less toxic than infliximab
Rituximab *	500-1000 mg every 1-6 months	Infections	Screen for viral hepatitis Check IgG level with chronic therapy	High risk for viral reactivation Can lead to IgG deficiency
Repository corticotropin injection *	40-80 units twice a week	Diabetes Hypertension Edema Anxiety	Monitor glucose and blood pressure	Most of toxicity is on day of injection
Hydroxychloroquine	200-400 mg qd	Loss of vision	Ocular exams every	Minimal impact

			6-12 months	on cardiac and neurologic disease

*Used reserved for patients who have failed prior treatments with steroids and/or anti-metabolites.
CBC: complete blood count; qd: daily; bid: twice a day; IgG; immunoglobin G;
Adapted from Obi O and Baughman RP.

Glucocorticoids: Prednisone and prednisolone are the two most commonly used drugs of this class, although hydrocortisone and dexamethasone have also been used. These drugs were approved for treatment in the 1950s based on reports of the utility of glucocorticoids and adrenal cortisol stimulating hormone (ACTH) (7;8). The dose of prednisone is unclear (9). Initial studies often gave 1 mg per kilogram body weight or an absolute dose of 40 mg a day. In a multi-center observational study, Broos et al observed that the response as assessed by improvement in FVC was not related to the dose of prednisone (5). In a retrospective study of sarcoidosis patients treated for worsening pulmonary symptoms, McKinzie et al found that 20 mg a day was as effective as higher doses in improving FVC (10). In cardiac sarcoidosis, a retrospective analysis found no benefit for giving more than 30 mg a day of prednisone (11). Prolonged prednisone therapy is associated with significant toxicity (12), including weight gain (5;13), diabetes, mood swings, osteoporosis, and cataracts (3). Therefore alternative agents which are steroid sparing have been investigated.

Methotrexate: Of the second line agents for pulmonary sarcoidosis, methotrexate has been the most widely studied. Original reports indicated that approximately two thirds of patients were able to reduce or stop prednisone use after six months of therapy (14;15). Subsequent other studies confirmed the effectiveness of methotrexate (16-18). Guidelines regarding dosage and monitoring sarcoidosis patients have been established (19).

Leflunomide is similar to methotrexate in action but with a different toxicity profile. It has been reported as effective in sarcoidosis as an alternative to methotrexate (20;21) and in some case has been used in combination with methotrexate (20). It is associated with less nausea and pulmonary toxicity (22). However, it can cause a peripheral neuropathy (23).

Azathioprine is a different anti metabolite which has been used to prevent solid organ rejection. It has been reported as effective as steroid sparing agent, although reported effectiveness ranges from 20 to 80% (17;24-26). Overall, azathioprine has more reported adverse events than methotrexate leading to more frequent withdrawal of the drug (17). The major complications are infections, increased gastrointestinal toxicity, and increased risk for myelodysplasia and malignancy (27-29).

Mycophenolate is another transplant medication used for sarcoidosis (30;31). It has less toxicity than azathioprine (28;32). However, one still has to monitor for infections. It has been proposed as more effective than other anti-metabolites for neurosaroidosis (33;34). However, one study found patients were significantly more likely to have mycophenolate stopped over time compared to methotrexate (35).

In the past, cyclophosphamide (CYC) has been used for treating refractory neurosarcoidosis (36;37). Cyclophosphamide is an alkylating agent associated with a variety of toxicities including bone marrow suppression, increased susceptibility to infection, fertility issues, hemorrhagic cystitis, increased risk of malignancy especially bladder cancer, and rarely pulmonary toxicity (38-42). Therefore the clinician should consider less toxic alternative medications whenever possible.

Anti-tumor necrosis factor (anti-TNF) antibodies: Inflximab is the most widely studied and used monoclonal antibody used for treatment of sarcoidosis. In a double blind placebo controlled trials, it was

found to be superior to placebo in treating chronic pulmonary sarcoidosis (43;44) and chronic cutaneous sarcoidosis (45). In addition, there have been several large retrospective series reporting its effectiveness in chronic skin (46), neurologic (47;48), and pulmonary manifestations (49;50). Biosimilars seem to have the same response rate as infliximab (51). Guidelines have been established to help identify which patients to treat, dosing, and monitoring (19). A major limitation of infliximab is increased risk for infections, especially tuberculosis (52), and allergic reactions (53).

Adalimumab is associated with less toxicity. However, the reported experience in sarcoidosis is less robust. It was found more effective than placebo in treating chronic cutaneous sarcoidosis (54). For pulmonary disease, there have been some case series reporting the drug was effective in chronic disease (55;56). Many clinicians feel adalimumab is less potent than infliximab in treating sarcoidosis (57). The drug can be an effective alternative when a patient develops a systemic reaction to infliximab (58).

Golimumab is another anti-TNF monoclonal antibody. In a double blind placebo controlled trial, the drug was no better than placebo in treating the disease (59). While this may have been because of the relatively lower anti-TNF dose of the drug, this drug is not recommended for most patients with advanced sarcoidosis. Etanercept, a TNF receptor antagonist, has also been shown to have a lower rate of response than that seen with the anti-TNF antibodies (60;61).

Rituximab was originally developed as a treatment for non Hodgkins lymphoma. Over the past ten years, it has been used increasingly in nonmalignant conditions, including sarcoidosis. Small case series and reports suggest the drug has a role as a third line therapy for advanced pulmonary, eye, neurologic, or cardiac disease (62-65). Current recommendation is to place patients who respond to rituximab on a maintenance regimen (64). The drug is associated with a lower rate of drug withdrawal than anti-TNF agents (66).

Repository corticotropin injection (RCI) was initially approved for sarcoidosis and many other conditions in the early 1950s. Originally it was felt the only mechanism of action was stimulation of the adrenal cortex to release cortisol and the drug was felt to be equivalent of oral glucocorticoids (8;67). Recent studies of non sarcoidosis diseases have suggested that RCI may have other mechanisms of action through alternative melanocortin receptors (68;69). There have been recent reports of the effectiveness of RCI as a steroid sparing agent in advanced sarcoidosis (70;71).

Hydroxychloroquine and chloroquine are antimalarial agents that have been used to treat sarcoidosis for many years (72). These agents have been useful to treat skin manifestations (73;74) and abnormalities of calcium metabolism (75;76). Hydroxychloroquine is the preferred agent at this time because of reduced ocular toxicity. However, it still may lead to significant vision loss and routine screening is recommended with this drug (77).

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