Cutaneous sarcoidosis therapy updated

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The widely accepted standard therapy for cutaneous sarcoidosis includes corticosteroids, antimalarials, and methotrexate. However, a better understanding of the basic immunopathogenic properties of sarcoidosis has elucidated a number of steps critical to the persistence and progression of disease that may be vulnerable to treatment by targeted therapy. This article reviews both standard and newer therapeutic options for cutaneous sarcoidosis. (J Am Acad Dermatol 2007;56:69-83.)

The goals of sarcoidosis treatment include: symptomatic relief, improvement in objective parameters of disease activity, and prevention of chronic disability caused by disease progression. Standard therapeutic interventions for cutaneous sarcoidosis have traditionally included topical, intralesional, and systemic steroids, as well as antimalarial drugs, methotrexate, and combinations of these agents. Because of the variable clinical response to standard therapy and the potential for associated toxicity, alternative treatment options are being explored. Similar to standard therapy, newer therapeutic modalities are based on the presumed pathogenesis of sarcoidosis, including specific cellular and cytokine abnormalities unique to sarcoid and the resultant development of tissue granulomas. The purpose of this article is to review the reported clinical experience with newer therapies for sarcoidosis with the caveat that evidence supporting the use of such agents is often anecdotal. Newer treatments should be entertained only when generally accepted therapy fails.

Abbreviations used:

APC:	antigen-presenting cells
FDA:	US Food and Drug Administration
ICAM-1:	intercellular adhesion molecule-1
IFN-γ:	interferon-gamma
IL:	interleukin
MGC:	multinucleate giant cell
TNFα:	tumor necrosis factor-alpha

ETIOPATHOGENESIS

The possible efficacy of any treatment is based on the assumed pathogenesis of sarcoidosis and the non-caseating granulomata that characterize the disorder. Granulomas are inflammatory responses that demonstrate a consistent element of mononuclear phagocytes and their derivatives (ie, epithelioid macrophages and multinucleate giant cells).[1] The inciting event in granuloma formation involves the deposition of persistent or poorly soluble antigenic material into tissues, where the latter is phagocytosed or endocytosed by APC in the form of macrophages or dendritic cells.[2] Processed antigenic material is transported to the cell surface where it activates $CD4^+$ T-cells. The granuloma continues to organize via the elaboration and secretion of certain key cytokines and chemokines.[3] Although a specific inciting antigen has not yet been identified for sarcoidosis, the immune response which leads to recognizable clinical lesions and functional impairment is of the type 1 variety: elevated IFN-γ, IL-2, and the Th_1 immunoregulatory monokine IL-12 characterize sarcoidosis.[4] TNFα, a critical cytokine in this process, augments the chemokine-associated recruitment of macrophages into the granulomatous lesion.[5] If the antigen(s) is/are removed via a granulomatous response, the disease may undergo remission. In chronic cases of granulomatous disease, the mononuclear cell inflammation persists and tissue consolidation and functional impairment ensue. While the majority of sarcoidosis patients achieve full recovery within months to years, a few individuals experience progressive disease with chronic disability.[6] The persistent granulomatous inflammation of chronic sarcoidosis prevents surviving parenchymal cells from reestablishing the normal tissue architecture,[7] with the ultimate consequence being progressive fibrosis.[2]

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Issues in the treatment of sarcoidosis

The treatment of sarcoidosis is complicated by issues of who should receive therapy, when therapy should be initiated and terminated, and when to transition from steroids (drugs of choice) to another modality.[8] The Joint Statement of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders outlined recommendations for cases in which treatment is warranted.[9] Indications for systemic therapy include: cardiac disease, neurologic disease, eye disease not responding to topical therapy, and hypercalcemia. Pulmonary sarcoid does not necessarily require treatment, but in cases with progressive respiratory symptoms or objectively demonstrated deterioration of lung function, therapy is justified. There are no inviolate guidelines for initiating therapy in cutaneous sarcoidosis, but treatment is typically initiated when widespread, progressive, disfiguring, or function-impairing skin lesions develop.[10]

Treatment: Based on immune dysregulation

The therapy of sarcoidosis is based upon the understood immunopathogenetic factors enumerated previously. However, it must be emphasized that a recommendation for any of the interventions discussed below is principally anecdotal, because the reported experiences with these agents are limited, often with isolated reports or small case series documenting use of a particular treatment. Therefore, although some of these therapies may indeed be promising interventions for sarcoidosis, there is an acknowledged lack of high quality (grade A or B) evidence-based medicine. The actions of the many treatments used to treat sarcoidosis are summarized in Table I.

STANDARD THERAPIES

Corticosteroids

Corticosteroids are the worldwide accepted standard treatment of sarcoidosis, although their exact mechanism of action in sarcoidosis is not known and there have been no double-blind, placebo controlled studies proving their efficacy. As with the newer agents used in sarcoidosis, the data supporting the use of corticosteroids is largely anecdotal. It has been proposed that corticosteroids suppress inflammation, and thus progressive granuloma formation, via their inhibitory effects on cytokine and chemokine synthesis.[11] Corticosteroids inhibit the transcription of pro-inflammatory signal molecules, such as TNFα, granulocyte macrophage-colony stimulating factor (GM-CSF), IL-1, IL-2, Il-3, IL-4, IL-5, IL-8, IL-11, IL-13, RANTES, Eotaxin, macrophage inflammatory protein 1 alfa, and monocyte chemoattractant proteins-1 and -3.[11] Nuclear factor kappa B (NFκB), the transcriptional activator of multiple genes involved in inflammatory responses, is inhibited by IκB proteins, and corticosteroids increase gene transcription of IκB.[12] In addition to having anti-inflammatory properties, corticosteroids have been reported to correct the imbalance between Th_1-associated and Th_2-associated cytokine and immunoglobulin production in sarcoidosis.[13]

In patients with mild lesions limited to the skin, ultrapotent topical steroid therapy may be all that is necessary. Topical steroids reported to be successful include halobetasol propionate and clobetasol propionate.[14,15] Typical dosing is twice a day application until lesions resolve. Topical steroids have the advantage of minimal systemic absorption. As with any topical treatment, application may be difficult if a large percentage of the total body surface is affected. Possible effects of topical steroids include skin atrophy and disturbance of the hypothalamic–pituitary–adrenal axis. The risk of both increases with the duration and potency of the treatment.

Volden[14] reported the complete remission of cutaneous sarcoidosis in three patients after 3 to 5 weeks of once-a-week application of clobetasol propionate under a hydrocolloid occlusive dressing that was changed weekly.[14] Because the medication was applied only once a week, the amount of topical steroid used was decreased by a factor of at least 20 while attaining the same success generally achieved by a twice daily application of a less potent agent. Atrophy was not observed in any of the 141 patients with chronic skin conditions treated in the study. Lupus pernio has also reportedly been treated successfully with twice weekly 0.05% halobetasol propionate.[15]

Lesions of sarcoidosis may also initially be treated with intralesional triamcinolone at concentrations of 3 mg/mL to 20 mg/mL, repeated every 4 weeks until flattening of the lesions occurs. Intralesional steroids are advantageous for small sarcoid papules and plaques, with concentration choice depending on lesional firmness and size.[16] In typical therapeutic dosage, intralesional steroids should not give rise to systemic effects.[17] Patients should be counseled that numerous injections may be necessary before achieving the desired result, and that recurrence of an apparently resolved lesion may happen once intralesional injections cease.[17] Possible side effects include hypopigmentation and atrophy.

Systemic corticosteroid therapy, usually delivered orally, should be reserved for severely disfiguring or destructive lesions, widespread involvement, or lesions that have proved refractory to localized