Treatment of Sarcoidosis

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KEYWORDS

• Sarcoidosis • Treatment • Corticosteroids • Steroid sparing • TNF antagonists • Prognosis • Patient preferences

KEY POINTS

- The treatment of sarcoidosis can be divided into the key questions of "whom to treat" and "how to treat".
- The decision to treat depends on the degree of organ impairment; threat to organ function; impact of symptoms on quality of life; and the extent, activity, and chronicity of disease.
- The patient's preferences and input are central in the process of deciding when and how to treat.
- Noninflammatory manifestations of sarcoidosis are commonly the salient feature, and treatment of them is usually not with immunosuppressive medications.
- The dosing, duration, and choices of steroids and nonsteroid medications should be adjusted empirically to the individual patient.

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease with large variability in presentation, disease behavior, and outcome. The cause of sarcoidosis and explanation for its wide phenotypic differences are not yet fully understood. Interaction between a presumed trigger and a genetically susceptible host is considered the mainstay of sarcoidosis pathogenesis. Genetic factors may play an important role in modifying the risk for the disease, its phenotype, and the outcome. As a result of the disease heterogeneity, treatment varies from none to a range of medications, including corticosteroids, cytotoxic agents, and biologic agents.[1–3] Despite important advances in the understanding of the disease, there is a paucity of evidence-based treatment protocols and data supporting a beneficial treatment effect on long-term outcomes.[4,5] Furthermore, despite more available therapies, some data suggest an increasing mortality trend over the past 2 decades.[6] Treatment of sarcoidosis should be tailored to the individual patient's needs; it encompasses balancing natural prognosis, severity, and impact of disease; likelihood of response to therapy; and potential side effects, leading to the central questions: whom to treat and how to treat?

WHOM TO TREAT

A decision to initiate treatment often implies that treatment will be necessary over the long term.[7,8] Thus, careful delineation of the goals of treatment is necessary. Some variables that should be considered include the expected prognosis; extent of disease; severity (impact on organ function and symptoms); whether it is active; and, most importantly, the opinion of the patient.

Prognosis

In many patients with sarcoidosis the disease resolves spontaneously. Even if the disease persists, it may not cause sufficient problems to require therapy. For example, in a survey of 500 patients

Disclosures: Dr D.A. Culver has received consulting fees from Mallinkrodt Pharmaceuticals.
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Clin Chest Med 36 (2015) 751–767
http://dx.doi.org/10.1016/j.ccm.2015.08.015

from 10 tertiary centers around the world, only 43% of patients who were still being seen at the centers were still using any therapy 5 years after diagnosis, similar to the proportion with persistent but untreated disease in those centers, which are also skewed to include the most severe case mix.[9] However, a substantial minority has chronic or progressive disease with concomitant morbidity, and a small proportion of these patients might even die from the disease. Having insight regarding the prognosis influences treatment decisions; if the risk of a poor outcome is high, there is a greater incentive to commence therapy. When instituting therapy, it is important to realize that not only the disease itself but also its treatments might (negatively) affect morbidity and mortality.

Reported mortalities in sarcoidosis vary from 1% to 7 % depending on the setting and population studied.[6,10–13] Swigris and colleagues[6] reported an increase in age-adjusted, sarcoidosis-related mortality of 50.5% in women and 30.1% in men over 2 decades. In the United Kingdom a 2-fold increased risk for death in sarcoidosis was reported, which was also greater in women.[14] A population-based cohort study in the United States uncovered a 2-fold increase in sarcoidosis-related hospitalizations in a decade.[15] However, it is debatable whether these numbers also reflect a possible better recognition of disease, an increase of severity, and/or an aging sarcoidosis population. In Europe and the United States deaths are primarily a result of progressive pulmonary fibrosis with subsequent respiratory failure.[16] Other causes are severe neurologic or cardiac involvement. In Japan, death is mostly attributed to cardiac involvement.[17,18]

Scadding's[19] landmark study from 1961 about the prognosis of sarcoidosis followed 136 patients with sarcoidosis for 5 years after their diagnosis. At the end of this study 97% of the patients with stage I disease and 58% with stage II were asymptomatic, whereas only 25% of the patients with stage III were asymptomatic.[19] These trends have subsequently been confirmed in other studies.[20–22] A commonly adopted clinical approach is the concept of 3 broad, partially overlapping groups: acute disease, which often resolves within 2 to 5 years of diagnosis; chronic disease, which persists beyond 5 years after diagnosis; and refractory disease, which progresses despite adequate therapy and is typically also chronic in duration.[23,24]

It is generally appreciated that patients with acute-onset disease have a good chance of spontaneous remission.[16,20,25,26] Löfgren syndrome, with its acute onset consisting of bilateral hilar lymphadenopathy, erythema nodosum, and polyarthritis, usually resolves spontaneously and generally does not require treatment.[22,27] Apart from Löfgren syndrome, the definition of acute sarcoidosis has varied considerably in the literature. In the past, disease resolution within 2 years was used as definition of the acute form.[23,25,28] However, several studies reported a substantial rate of resolution of disease between 2 and 5 years from diagnosis, which has led to the redefinition of chronic as that disease persisting after 5 years.[24,26,29,30] Nevertheless, persistence of active inflammation more than 2 years from diagnosis reduces the chances of resolution substantially.[24]

Studying the natural history of sarcoidosis is limited by differences in case identification, dissimilarities in racial background, differences in techniques for assessing organ involvement, and the confounding effects of variable treatment.[8,19,27,28,31,32] In the past decade, several approaches have been proposed to phenotype patients with sarcoidosis in relation to clinical outcome.[9,33–37] Recently, Walsh and colleagues[37] showed that a combination of a composite physiologic index and high-resolution chest computed tomography findings of fibrosis and pulmonary artery/aorta size ratio predicted mortality. A disadvantage of this approach is that the model focuses primarily on advanced disease, and therefore does not have clear-cut relevance for predicting the likelihood of a poor outcome at the time of sarcoidosis onset.

Until now, no study has comprehensively established which features most strongly determine the chance of spontaneous resolution or of serious organ involvement. Besides ascertainment bias related to referral patterns and evolving technologies, there have been few attempts to systematically assess manifestations and then to follow patients for an adequate length of time to conclusively define which features independently carry the most weight for long-term prognosis. As an example, several studies have suggested that African Americans have a worse prognosis than white Americans in the United States.[27,38,39] However, multivariable analysis in a large US study suggested that the worse prognosis in African Americans may relate primarily to their greater frequency of extrapulmonary organ involvement, rather than to race itself.[7] Some of the features that have most commonly been associated with a worse prognosis are listed in **Table 1**.

Effect of Treatment on Natural History

Granuloma formation in sarcoidosis is thought to result from interaction of an environmental antigen and a genetically susceptible host. This interplay