Corticosteroid-Sparing Drugs in Sarcoidosis: How Should We Assess Them?

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The current treatment approach to sarcoidosis is not optimal. Corticosteroids are considered the drugs of choice for sarcoidosis because they work reliably and quickly. In addition, corticosteroids are cheap, especially in comparison to biologics. Despite the potent anti-sarcoidosis effects of corticosteroids, their side effects often end up causing more harm than good in sarcoidosis patients. Chronic corticosteroid therapy in sarcoidosis cohorts has been associated with worse quality of life [1], more health care utilization [2], and significant comorbidities [3]. For these reasons, effective and non-toxic corticosteroid-sparing and corticosteroid-replacing therapies for sarcoidosis are needed. Although such therapy is a common desire of sarcoidosis patients, the United States Food and Drug Administration (FDA) has not yet accepted the corticosteroid-sparing capacity of an anti-sarcoidosis drug as an adequate labelling claim.

In this issue of *Lung*, Friedman and colleagues present an open-label pilot trial of tofacitinib, a Janus protein tyrosine kinase (JAK) inhibitor, as a corticosteroid-sparing therapy in 5 sarcoidosis patients [4]. There is both immunologic and clinical support for such therapy, as the JAK-signal transducer and activation of transcription (STAT) signaling pathway is activated in inflammatory cells and tissues of sarcoidosis patients [5], and case reports have shown tofacitinib to be a useful treatment for the disease [6].

In the current trial, the authors found that 3 of 5 corticosteroid-dependent pulmonary sarcoidosis patients who received tofacitinib 5 mg twice daily were able to meet the primary trial endpoint of a $\geq 50\%$ corticosteroid dose reduction after 16 weeks of therapy. The trial involved a very small number of patients, was open label and without a control group. One patient developed worsening

neurosarcoidosis, a serious manifestation of the disease. Another patient has lost to follow up, so we are unaware of this patient's outcome. Nonetheless, despite these deficiencies, this study suggests that tofacitinib may have significant corticosteroid-sparing potential in a subgroup of sarcoidosis patients. Probably the strongest evidence for anti-sarcoidosis activity of tofacitinib in this study occurred in the extension portion of the trial, where the three patients who responded to tofacitinib and continued receiving the drug for a year remained off corticosteroids.

Although the corticosteroid-sparing effect of anti-sarcoidosis drugs has been evaluated in previous trials, [7] this has never been used as a primary study endpoint. For such studies to yield meaningful results, they must be carefully designed to account for the natural history of sarcoidosis. Specifically, the following clinical features of sarcoidosis must be considered:

1. The minimum effective dose of corticosteroids for sarcoidosis can be precisely defined, but it differs from patient to patient and for different organs [8]. Furthermore, the minimal effective corticosteroid dose does not seem to vary with time [8]. Therefore, for the results of a corticosteroid-sparing trial to be meaningful, the minimum effective dose must be established for the target organ in every patient. In terms of this trial, patients were enrolled who were receiving a maintenance dose of 15 to 30 mg/day of prednisone. It has been shown in a study of 36 patients who had an exacerbation of pulmonary sarcoidosis that none had an exacerbation on a maintenance dose of > 10 mg/day of prednisone and only 22% had an exacerbation on > 5 mg/day of prednisone [9]. Therefore, at least in terms of judging the corticosteroid-sparing effect of tofacitinib in this cohort, defining success by reducing the prednisone dose in half from a 15–30 mg/day starting dose would be inappropriate.

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2. Recurrent granulomatous inflammation from sarcoidosis typically takes weeks to several months to become evident. Therefore, there is a lag between tapering corticosteroids below the lowest effective dose and a clinically evident sarcoidosis relapse [8]. Given the corticosteroid tapering regimen in this trial where all but one patient were not tapered below 10 mg/day of prednisone until 8 weeks, it is very unlikely that patients would have clinically relapsed by 16 weeks.
3. Chronic sarcoidosis is not necessarily a life-long disease and often has a natural course spanning 5 to 10 years [10, 11]. In some series, approximately 20 percent of such patients can discontinue chronic corticosteroid therapy without developing a relapse [10]. Therefore, rigorous corticosteroid-sparing trials require a control group.

I commend these authors for conducting and publishing this trial which suggests a potential role for tofacitinib in the treatment of sarcoidosis. Hopefully, drug agencies will appreciate the importance that patients place in the development of corticosteroid-sparing medications. In the meantime, it behooves us to design rigorous protocols so that the corticosteroid-sparing activity of anti-sarcoidosis drugs can be reliably measured.

Compliance with Ethical Standards

Conflict of interest The author has received research funding for his institution from Mallinckrodt. He is a consultant for Star Therapeutics.

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