Less Tx May Be Better in Pulmonary Sarcoidosis

Most sarcoidosis will resolve within the first 5 years, regardless of whether one treats it.

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

VANCOUVER, B.C. – Contemporary management of pulmonary sarcoidosis is moving away from hard clinical targets and toward patients' self-reported well-being and goals, according to Dr. Daniel A. Culver, a pulmonologist at the Cleveland Clinic.

Physicians may treat sarcoidosis for a variety of reasons, and research is helping to sort out which of them are valid, he said at the meeting.

One reason might be to improve radiographic or physiologic parameters. In particular, the Scadding stage of a patient's chest x-ray at presentation has been used for about 50 years to estimate prognosis and the need for treatment.

"But in fact there are a number of pieces of data coming out now that suggest that the chest x-ray may not be the most ideal way to measure how things are going to go for patients," he commented.

In one study, for example, half of patients with pulmonary sarcoidosis were rated as having a better chest x-ray during an exacerbation as compared with before, despite their worsening symptoms and spirometry (Respirology 2008;13:97-102).

The evidence for initiating treatment with steroids for sarcoidosis patients 'really is not very strong, despite the fact that steroids have been used for about 60 years now.'

Another reason for undertaking treatment might be to improve patients' symptoms, according to Dr. Culver.

In this regard, a recent review has described a so-called sarcoidosis penumbra, a collection of disease-related issues that affect patients' well-being but are often not well captured by tests physicians rely on (Semin. Respir. Crit. Care Med. 2010;31:501-18). For instance, two in every three patients have depression, and one in six has sleep apnea.

"This took us a long time as sarcoidologists to recognize, that it's not the x-ray and vital capacity that the patients care about," but rather their daily ability to function and enjoy life, he commented.

"To optimally treat sarcoidosis, one of the new things we are discovering is that we need to ask the patients the questions that get to these sorts of issues and target our treatment to these sorts of issues," Dr. Culver said. "Going forward … for both immunosuppressive therapy and the treatment of sarcoidosis in general, we are going to see it more focused on patient-centered outcomes and quality of life rather than things that we'd all like to measure, like the vital capacity."

Another reason that physicians may treat sarcoidosis is to alter the natural history of the disease and prevent fibrosis.

But "most sarcoidosis will resolve within the first 5 years, at least radiologically," Dr. Culver noted, and current evidence suggests treatment does little to alter this trajectory.

In one study, 39% of patients with stage 2 or 3 disease on chest x-ray had neither progression nor improvement during a 6-month period. When these stable patients were assigned either to immediate treatment with a fairly aggressive regimen of prednisolone or to as-needed treatment only if spirometry showed deterioration, just 19% of the latter group required treatment during the next 5 years (Thorax 1996;51:238-47).

"If you can hold off on treating, you may be able to prevent side effects from medicines … and still have a patient who has their disease spontaneously resolve," he commented.

That said, the as-needed treatment group had a smaller improvement in forced vital capacity (FVC), and there were some other potentially important differences in outcomes between groups.

"Suffice it to say that right now, we don't think that steroid therapy given preemptively has a tremendous impact on the natural history of the disease," Dr. Culver commented. "This is probably the best study that addresses this question, but this doesn't necessarily resolve the issue."

Finally, physicians may initiate treatment for sarcoidosis because they feel compelled to do something, according to Dr. Culver.

"It makes us feel better when we go home at night: We have done something for the patient who came to see us," he commented. "But the evidence for this [practice] really is not very strong, despite the fact that steroids have been used for about 60 years now."

A recently proposed algorithm for treating pulmonary sarcoidosis draws on all of these accumulated data and recommends symptom assessment as a first step (Semin. Respir. Crit. Care Med. 2010;31:501-18).

"If the symptoms are relatively mild or modest – and this requires a discussion with the patient – then I think observation is completely reasonable," Dr. Culver said.

In more severe cases, the algorithm proposes short-course, moderate-dose therapy with prednisone 20-30 mg daily for 3-4 weeks, as supported by several studies, including a recent one among patients with acute exacerbations (Am. J. Med. Sci. 2010;339:1-4).

In other words, "be less aggressive with your steroid dosing," he recommended. "You can really get away with shorter courses, with lower doses than we have been using in the past."

For patients who have a good response, the goal is to taper to 10 mg daily or less, a practice endorsed by a Delphi consensus study of sarcoidosis management (Respir. Med. 2010;104:717-23).

"That's evolving as an important target for long-term management of sarcoidosis patients," he noted, and it also helps minimize steroid adverse effects.

When patients have an inadequate response to prednisone or are unable to reduce the dosage to 10 mg daily, the algorithm suggests adding an immune modulator (methotrexate, azathioprine, leflunomide, or mycophenolate) to therapy.

"The choice of immune modulators … is really dealer's choice," Dr. Culver commented. "Suffice it to say that it's most important that you become comfortable with something and you are used to how to use it, more so than necessarily exactly which one to use."

There have been few head-to-head comparisons of these agents, although methotrexate is by far the agent preferred by U.S. physicians treating sarcoidosis, partly because it has been the best studied.

"That's the drug that we use as our second-line agent," Dr. Culver noted. "The reason that we like methotrexate is it seems to work pretty well, it's pretty inexpensive and pretty reliable, and it's not hard to get through the insurance company."

Data from his institution show that leflunomide also works well. A review of 40 patients with pulmonary sarcoidosis found they had an improvement in FVC within 6 months of starting this drug ($P = .01$), as well as a reduction in the average prednisone dose to 5 mg daily.

"So we have really moved leflunomide to the next agent in our algorithm after methotrexate," he said.

Infliximab is the only agent that has been shown to be efficacious in a double-blind, randomized controlled trial of patients with sarcoidosis, according to Dr. Culver.

In unselected patients, infliximab is associated with just a 2.5% improvement in percent predicted FVC (Clin. Chest Med. 2008;29:533-48, ix-x) – or about that seen with steroids. But among the subset having more severe lung disease, with an FVC of less than 69%, there is a roughly 3.25% improvement. The improvement was 6% in the randomized trial (Sarcoidosis Vasc. Diffuse Lung Dis. 2006;23:201-8).

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"So, in fact, we think for patients failing cytotoxic agents that infliximab is a nice option," Dr. Culver commented.

And studies are helping to identify which patients are most likely to benefit from infliximab: those who have had disease for more than 2 years, have worse dyspnea (a Medical Research Council dyspnea score of at least 2), lower FVC, poorer quality of life (assessed with the St. George's Respiratory Questionnaire), reticulonodular changes on their chest x-ray, or an elevated C-reactive protein level.

"In fact, these are some of the same entry criteria that are being used for the current trial of biologics in sarcoidosis, trying to target that more severe patient population," he noted.

In concluding, Dr. Culver advised physicians to establish and keep in mind the goals of treatment, and to remember the chronic nature of sarcoidosis.

"If I can leave you with one thing, the message is … you have to sit and talk to your patient and find out what's important to them, what do they want to accomplish," he said.

"That's the best thing that you can do as you think about treating your patient longitudinally, because remember, you are not treating this as if it's an infection, you are treating this as if it's hypertension that needs to be controlled in the long term."

Dr. Culver reported having affiliations with the biotechnology and pharmaceutical companies Centocor (manufacturer of infliximab), Takeda, and Actelion. ■