ASK THE EXPERT

Pulmonary Fibrosis in Systemic Sclerosis

Pulmonary complications are the leading cause of morbidity and mortality in systemic sclerosis or systemic scleroderma.

Pulmonary fibrosis in particular is the leading cause of systemic sclerosis/scleroderma deaths. Some degree of progressive scarring is thought to occur in up to 70% of patients with systemic sclerosis/scleroderma and cause severe restrictive lung disease in approximately 15% of patients. The condition, which can lead to respiratory failure and, potentially, pulmonary artery hypertension, presents a therapeutic challenge because its development and progression are unpredictable and its early symptoms overlap with those of many other conditions.

BY KEVIN BROWN, M.D.

In this month's column, Dr. Kevin Brown, director of the interstitial lung disease program of the National Jewish Medical and Research Center in Denver, discusses new developments in the diagnosis and management of pulmonary fibrosis in systemic sclerosis patients.

Rheumatology News: What is the proposed mechanism for the pathogenesis of pulmonary fibrosis in systemic scleroderma?

Dr. Brown: Nobody knows why it occurs, but the presumption is that it is related somehow to the same kind of fibrosis that affects the skin in cutaneous scleroderma. Studies have shown that patients with certain types of serologic abnormalities—certain patterns of autoantibodies—might be more likely to develop pulmonary fibrosis than other patients, but as far as we can tell, it is not restricted to any of the scleroderma subtypes. It can be a complication of all of the subtypes.

RN: What symptoms/clinical presentation should the clinician be aware of?

Dr. Brown: Clinically, it depends on how early in the course of the disease you're talking about. Patients generally present in one of a handful of ways. Shortness of breath is the most common symptom and some patients will have a cough. The problem is that pulmonary fibrosis is not the only cause of these nonspecific symptoms. Sometimes there are physical exam findings when listening to the lungs, but generally these are identified later in the disease.

RN: How is a suspected diagnosis confirmed?

Dr Brown: There are two ways to screen for pulmonary fibrosis: lung function testing and high-resolution computed tomography. Some physicians will scan every patient and do pulmonary testing at the time of scleroderma diagnosis; others do it only when they think there's a reason to. Often it comes down to the fact that we're dealing with two subspecialties here. If a pulmonologist is looking at the patient, he or she is probably going to be more likely to evaluate the lung, while a rheumatologist may or may not, depending on his or her mindset. Recently there has been more of a push for going ahead and evaluating the lungs at diagnosis, particularly because fibrotic lung disease and pulmonary artery hypertension are the most common causes of morbidity and mortality in scleroderma. Also, there have been some treatment developments recently that are showing some promise, so the thought is to catch the lung complications early and to treat them aggressively.

RN: What are some of the key management considerations for scleroderma patients with pulmonary fibrosis?

Dr. Brown: There was an important paper within the past year suggesting that the use of cyclophosphamide over 12 months may slow or slightly improve the loss of lung function that one might expect in patients with interstitial lung disease. The study showed at least three important things: that cyclophosphamide improves lung physiology in affected patients, that it lessened dyspnea, and that it improved quality of life over 12 months when compared with placebo. The finding also supports the argument for early lung screening in scleroderma patients. When there was no effective therapy for the condition, the argument against screening was "What's the point?" But now that we know there is pretty good evidence that therapy can modify outcome in patients, the general feeling is that the sooner the better.

There are also some other medications being studied. A couple of papers have suggested that mycophenolate mofetil (CellCept) might work, and there are anecdotal reports of others, but none of these has been studied as long or as well as cyclophosphamide.

RN: What are the management considerations associated with cyclophosphamide therapy?

Dr. Brown: Cyclophosphamide is a potent immunosuppressant, so it requires careful monitoring. It's mostly used as a chemotherapeutic agent in cancer patients. We use lower doses when treating lung disease, but some of the risks remain, including, in the short term, lowering of the white blood cell count, anemia, and liver test alterations. The big concern is that the breakdown products are very irritating to the bladder and can cause bleeding, hematuria, hemorrhagic cystitis, and, rarely, cases of bladder cancer. There also is the risk of long-term hematologic malignancies if the drug is taken for a long period of time. Some of that information has been generated from high-dose cancer studies. We use the drug differently for the lungs, but the risks still need to be considered.

Right now, 12 months is the standard duration of therapy. The longer a patient is on the drug, the more likely it is that he or she will accumulate the risk for long-term toxicity.

RN: Are there any new therapies on the horizon?

Dr. Brown: There are a number of new studies being planned, including a proposal to study cyclophosphamide followed by mycophenolate mofetil that is currently being reviewed [by the National Institutes of Health]. What's most promising is that there are now a number of people thinking about this problem and studying it. ■

DR. BROWN *is director of the interstitial lung disease program, vice chair in the department of medicine, and acting head of the pulmonary/critical care medicine division at the National Jewish Medical and Research Center in Denver.*

Small Study: Infliximab Worked in Multisystem Sarcoidosis

BY BRUCE JANCIN
Denver Bureau

SALT LAKE CITY — Infliximab is a highly effective and safe therapy for patients with multisystem sarcoidosis refractory to conventional immunomodulatory agents, Dr. Ghulam Khaleeq said at the annual meeting of the American College of Chest Physicians.

The tumor necrosis factor–α inhibitor is generally well tolerated in this setting, with minimal side effects, added Dr. Khaleeq of Drexel University, Philadelphia.

He presented a retrospective observational study involving 20 patients with refractory multisystem sarcoidosis in an outpatient pulmonary medicine practice who were placed on infliximab (Remicade) because of persistent symptoms or side effects on prednisone, methotrexate, and/or hydroxychloroquine.

The patients' mean age at the start of infliximab was 45 years, with a prior 11-year history of sarcoidosis since diagnosis. Seventeen of the 20 patients were women; 16 patients were African American. Seventeen had lung involvement, and 8 had CNS disease. Skin, joint, or lung manifestations were seen in 13, 11, and 9 patients, respectively. In addition, 7 patients had ocular disease, 5 hepatic, 4 bone, 3 sinus, and 2 renal.

The pulmonary disease was generally well controlled with conventional therapy. The chief reason patients went on infliximab was refractory bone or brain disease.

Sarcoidosis is an off-label use for infliximab. Dr. Khaleeq and his colleagues dosed the intravenous chimeric IgG monoclonal antibody using the standard protocol for Crohn's disease: 5 mg/kg at weeks 0, 2, and 6, then every 6 weeks thereafter.

All patients had marked and rapid improvement in symptoms. The gains have been maintained during an average of just less than 2 years of therapy. Nearly all patients were on at least 10 mg/day of prednisone at the outset, but by 6 months four patients had discontinued steroids and the rest had reduced their dosage.

Infliximab is generally well tolerated in refractory sarcoidosis patients.

DR. KHALEEQ

Of two patients on 60 mg/day of prednisone at baseline, one was on 20 mg at 6 months and the other was off the steroid entirely. In addition, six patients were off methotrexate and three patients were off hydroxychloroquine.

Four patients developed mild side effects on infliximab: One had frequent upper respiratory tract infections, one developed leg pain, another experienced fatigue and night sweats, and one patient developed hemiplegia, which resolved with stress-dose steroids. No one has had to discontinue infliximab.

Audience members with expertise in using infliximab for refractory sarcoidosis confirmed Dr. Khaleeq's impression that when patients are refractory to conventional therapies, they are generally refractory at sites other than the lung.

The discussion period featured a lively debate about the value of prescribing methotrexate with infliximab to prevent formation of antibodies to the chimeric monoclonal antibody and subsequent anaphylaxis. One camp asserted that this common practice is based on unconvincing data and really isn't necessary. Dr. Robert P. Baughman took a somewhat different view.

"I think you can reasonably make an argument for stopping an immunomodulator if the patient is doing well on infliximab," according to Dr. Baughman, professor of internal medicine at the University of Cincinnati. "Our bias is that methotrexate is not a very toxic drug if given in appropriate doses, so we tend to keep people on it. But certainly you have to ask if it's doing anything, especially after you get past that first 6 to 12 months. After that, the risk of anaphylaxis is going to be pretty low. Most cases occur by the fourth or fifth dose."

Dr. Baughman was the principal investigator in a recent positive phase II randomized, double-blind, placebo-controlled trial of infliximab in 138 patients with chronic pulmonary sarcoidosis (Am. J. Respir. Crit. Care Med. 2006;174:795-802). ■