Bosentan Begat New Era in Sclerosis

BY BRUCE K. DIXON
Chicago Bureau

CHICAGO — A new era is emerging in the management of systemic sclerosis, and within 5 years the number of available drugs should resemble the sort of variety seen with other rheumatic disease treatment options, Dr. John Varga said at a symposium sponsored by the American College of Rheumatology.

Dr. Carol Black and her fellow investigators "looked at a systemic sclerosis population with associated pulmonary artery hypertension [PAH] before and after 2002 to determine the effect of introducing the endothelin-1 receptor antagonist," in a retrospective study, said Dr. Varga, who is the Gallagher Research Professor in Rheumatology at Northwestern University, Chicago.

Bosentan is being evaluated in systemic sclerosis-associated interstitial lung disease.

DR. VARGA

The investigators, of University College Medical School, London, divided patients into a "historical" control group of 47 patients studied before 2002 and a "current treatment era" group of 45 patients studied after 2002.

The historical cohort received basic treatment, including diuretics, digoxin, oxygen, and warfarin, and 27 patients in the group also received prostanoids. The "current treatment era" group got bosentan.

Survival rate in the historical control group was 68% at 1 year and 47% at 2 years, whereas in the current era treatment group survival was 81% and 71%, respectively, according to Kaplan-Meier analysis. In addition, vascular resistance was stabilized in the bosentan cohort (Heart 2006, Jan. 31;doi 10.1136/hrt.2005.069484 [Epub ahead of print]).

"These data are very helpful but are preliminary, and I think it will be very important to follow these patients to see how much of an improvement they [make]," said Dr. Varga. Blocking endothelin-1 may do more than just block vasoconstriction. Bosentan, through vascular proliferation or the production of new blood vessels, may promote vascular repair, according to the study.

Another promising drug in the same class as bosentan is sitaxsentan, which has received approval under the FDA's orphan drug program, but is not yet clinically available in the United States. Bosentan is currently being evaluated in patients with systemic sclerosis-associated interstitial lung disease, noted Dr. Varga.

In a recently completed multicenter, placebo-controlled study of patients with early disease and alveolitis, treatment with oral cyclophosphamide yielded significant benefit at 12 months.

Data from the Scleroderma Lung Study also show that bronchoalveolar lavage (BAL) did not influence outcome, which Dr. Varga said contradicts earlier findings from retrospective studies and calls into question the role of BAL.

Another promising avenue in treating sclerosis-associated PAH is to enhance nitric oxide by using phosphodiesterase inhibitors. "In a published British study, investigators compared sildenafil to endothelial receptor antagonists and the data are similar in terms of short-term symptomatic improvement and better exercise tolerance," said Dr. Varga. Sildenafil has received FDA approval for the treatment of PAH (Am. J. Respir. Crit. Care Med. 2005;171:1292-7).

Prostacyclines also are available for treating PAH. "Inhaled iloprost, a stable analog of prostacycline, leads to clinical benefits. So there are a number of drugs and it's currently difficult to know where they fit in clinically." Autologous hematopoietic stem cell transplantation (HSCT) induced marked improvement or complete remission in animal models of autoimmunity, as well as in some patients with lupus and rheumatoid arthritis, said Dr. Varga. A large multicenter trial comparing HSCT with monthly cyclophosphamide in patients with severe sclerosis is underway.

Another approach, explained Dr. Varga, may be to target autoimmunity and prevent the initial activation of fibroblasts using anticytokine antibodies to connective tissue growth factor or transforming growth factor β. This is similar to the approach in rheumatoid arthritis treatment using tumor necrosis factor–α inhibitors, said Dr. Varga. "A clinical trial with an antichemokine antibody looking at early lung diseases in scleroderma is planned for later this year," he said. ■

JOINT DECISIONS

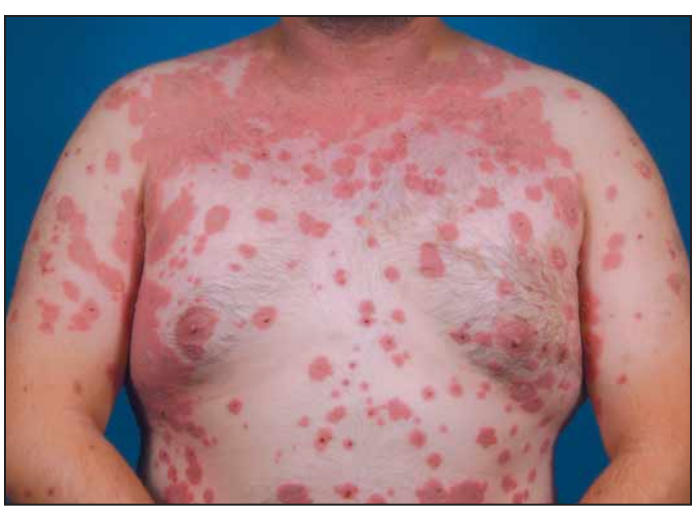
Diagnosis: Bullous Pemphigoid

A 27-year-old otherwise healthy man presented with a 2-day history of pruritic blisters that were scattered on the trunk and proximal extremities. Two weeks after admission, oral mucous membrane lesions developed, the patient complained of pain on swallowing, and the skin involvement had increased to 90% of the body surface area. Histology revealed a subepidermal blister with a superficial, perivascular infiltrate with eosinophils, lymphocytes, and neutrophils. Numerous eosinophils were present in the blister cavity, and direct immunofluorescence showed linear staining of IgG, IgA, and C3 along the basal membrane. ELISA showed the presence of IgG autoantibodies against bullous pemphigoid antigen 2 (BPAG2, 180 kd), but none against bullous pemphigoid antigen 1 (BPAG1, 230 kd), said Dr. Amanda S. Buchau of the dermatology department at Heinrich Heine University, Düsseldorf, Germany with mucosal involvement in 10%-20% of cases. The condition may result from an increased expression of anti-BP-180 autoantibodies, which are considered a marker of poor prognosis in bullous pemphigoid.

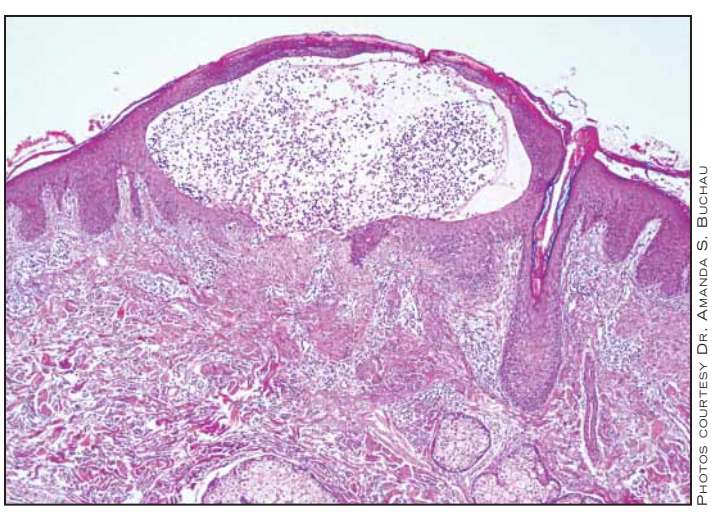
This patient was treated with methylprednisolone up to 160 mg/day for 3 weeks, along with pulse cyclophosphamide 1,000 mg, without response. His antibody titer also remained very high, so plasmapheresis was performed. Treatment with 250 mg/day of prednisone and 1 g of mycophenolate mofetil twice daily stabilized the disease, and he was given ciprofloxacin, dicloxacillin, and piperacillin to prevent infections, as well as antihistamines and topical steroids to alleviate pruritus.

Dr. Buchau presented this case at a congress on skin, rheumatism, and autoimmunity held in Abano Terme, Italy.

—Nancy Walsh



The otherwise healthy man presented with a 2-day history of pruritic blisters across the trunk and proximal extremities.



Histology revealed a subepidermal blister with a perivascular infiltrate with eosinophils, lymphocytes, and neutrophils.

PHOTOS COURTESY DR. AMANDA S. BUCHAU

Rituximab Lowers ANCA In Wegener's

BY PATRICE WENDLING
Chicago Bureau

MIAMI BEACH — B-cell depletion with rituximab may be a useful treatment option for severe refractory Wegener's granulomatosis when patients are intolerant or have a contraindication to cyclophosphamide, Dr. Ulrich Specks said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Rituximab appears safe and effective for inducing and maintaining remission in patients with active severe antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, Dr. Specks and colleagues at the Mayo Clinic, Rochester, Minn., reported.

In February, Genentech Inc. received an orphan product designation for rituximab (Rituxan) for the treatment of ANCA-associated vasculitis including Wegener's, microscopic polyangiitis, and Churg-Strauss syndrome.

In Dr. Speck and colleagues' prospective, open-label, industry-supported pilot trial, 10 patients with active disease received oral prednisone 1 mg/kg per day and four weekly infusions of rituximab 375 mg/m^2. Circulating B lymphocytes disappeared from peripheral blood by 4 weeks in all patients, and remained undetectable for 6-12 months (Am. J. Respir. Crit. Care Med. 2006;173:180-7).

Clinically, all patients went into complete remission by 3 months, and were tapered off prednisone by 5.5 months, Dr. Specks said. One patient experienced a clinical flare and was put back into remission after retreatment with rituximab and prednisone.

ANCA titers dropped in all patients, and generally did not rise until after B cell reconstitution. By 12 months, B cells had returned in 9 of 10 patients. "We didn't observe relapses in the absence of B cells and didn't observe relapses in the absence of ANCA-titer increases," he said. Overall, the regimen was very well tolerated. There was only 1 infusion reaction, 1 case of influenza, 13 urinary tract infections in five patients, 2 herpes zoster cases, and no antichimeric antibodies developed.

Although the results compared well with earlier published small and single-case trials, larger studies should be conducted to determine whether rituximab should replace cyclophosphamide as the standard of care, he said.

While Dr. Specks gave rituximab a conditional nod, he noted that antitumor necrotic factor therapy provides no added benefit on top of standard therapy and should be avoided in patients who have received cyclophosphamide. He cited the high rates of adverse events, particularly the increased incidence of cancers observed in the Wegener's Granulomatosis Etanercept Trial, in which he was an investigator. ■