Imatinib Mesylate Said to Offer Promise for Scleroderma Patients

Tyrosine kinase inhibitor appears to reduce skin thickness and improve lung function.

BY AMY SCHONFELD

EXPERT ANALYSIS FROM A RHEUMATOLOGY MEETING SPONSORED BY NEW YORK UNIVERSITY

NEW YORK – Targeted inhibition of tyrosine kinases with the use of imatinib mesylate is one of the most promising new areas of therapy for scleroderma, according to Dr. Jonathan Kay, who gave a "Year in Review" update on scleroderma therapy at the meeting.

"We know that imatinib mesylate reduces bone marrow fibrosis in patients with chronic myelogenous leukemia, the disease for which it is indicated and FDA [Food and Drug Administration] approved," said Dr. Kay, who is director of clinical research in the rheumatology division at the University of Massachusetts, Worcester. "It also strongly inhibits transcription and translation of extracellular matrix proteins by dermal fibroblasts."

In one study of 30 patients, treatment with imatinib led to improvements in several quality of life measures.

DR. KAY

Dr. Kay described the results of a study published online (Ann. Rheum. Dis. 2011;70:1003-9).

In this phase IIa, open-label, single-arm clinical trial, 30 patients with diffuse cutaneous systemic sclerosis (dcSSc) were treated with imatinib 400 mg daily and monitored monthly, making it the largest prospective trial of imatinib in dcSSC reported to date. Twenty-four patients completed a year of imatinib therapy. Patients were stratified according to disease duration, with 20 in the early-disease group (time of onset of first symptom less than 4 years) and 10 in the later-disease group (time of onset of first symptom 4-10 years).

To assess cutaneous symptoms, the investigators used the modified Rodnan skin score (MRSS), a standard outcome measure of skin disease in systemic sclerosis, which is calculated by summation of skin tethering scores at 17 different body sites. Over the 12-month treatment, the MRSS decreased by 22.4%. Significant changes were noted within 6 months of treatment. Similar improvements were noted regardless of the stage of the disease.

Blinded dermatopathologic analysis showed that the median skin thickness decreased significantly with treatment. Before treatment, the skin specimens exhibited changes characteristic of scleroderma, including thick and hyalinized collagen bundles with decreased interstitial spaces. After treatment, 7 of 10 specimens showed a qualitative decrease in the thickness of collagen bundles and an increase in interstitial spaces. Significant increases in the number of hair follicles and eccrine glands were also noted. Dermatopathologic changes correlated with MRSS scores.

Lung function, as assessed by forced vital capacity, improved significantly over the course of the year. When patients were divided into those in whom interstitial lung disease (ILD) was present or absent, significant improvements were observed only in those without ILD (mean increase 10.7%) compared to those with ILD (mean increase 2.1%).

Treatment with imatinib also led to improvements in patient-reported and physician-reported quality of life measures, such as the visual analog scale (VAS) global, VAS shortness of breath, VAS pain, mental component of Short Form-36 Health Survey, and physician global assessment.

Eighty percent of the patients were able to complete the trial, although 83% required a dose adjustment. The median imatinib dose taken was 300 mg daily. A total of 171 adverse events were reported possibly, probably, or definitely related to imatinib, and 97.6% were grade 1 or 2. The most common side effects were edema (80%), nausea (73%), and myalgia (67%), but these were felt to be manageable and tolerable. There were 24 serious adverse events.

One patient with severe ILD and pulmonary artery hypertension died, but this was not believed to be medication related. One patient was repeatedly hospitalized for hemorrhagic cystitis, which was thought to be due to a preexisting condition. While cardiac toxicity is a general concern with imatinib treatment, two patients developed cardiac issues that were not thought to be imatinib related.

Dr. Kay pointed out that because this was an open-label study, the findings cannot be definitively attributed to effects of the medication. "Results have been promising with the use of tyrosine kinase inhibitors to treat fibrosing conditions such as nephrogenic systemic fibrosis and scleroderma, but we need randomized, double-blind controlled trials," he said.

Dr. Kay has demonstrated a rapid response to imatinib in two patients with nephrogenic systemic fibrosis, a disabling condition cause by gadolinium that is characterized by rapidly progressing fibrosis (Arthritis Rheum. 2008;58:2543-8). He suggested that imatinib may work best for conditions that are predominantly proliferative rather than inflammatory.

Dr. Kay also reviewed other notable recent publications on scleroderma and fibrosis. Bosentan is a dual endothelin receptor antagonist, which is FDA-approved for the treatment of pulmonary arterial hypertension. A randomized controlled trial (RCT) on the use of bosentan for scleroderma indicated that the agent may be a useful adjunct for the treatment of scleroderma digital ulcers (Ann. Rheum. Dis. 2011;70:32-8).

The study showed that bosentan reduced the occurrence of new digital ulcers but had no effect on digital ulcer healing. Data from another study (Arthritis Rheum. 2010;62:2101-8) do not support bosentan as therapy for interstitial lung disease due to scleroderma.

An RCT published online evaluated methotrexate in a group of 85 children with active juvenile localized scleroderma, and found it to be effective and well tolerated (Arthritis Rheum. 2011 [doi:10.1002/art.30264]).

Over a 12-month period, infrared thermography of target lesions showed significant benefits from methotrexate treatment, beginning at 9 months. The proportion of patients without disease flare was significantly higher among those treated with methotrexate, but the number of patients with new lesions did not differ between the two groups. Many of the side effects were attributed to concomitant corticosteroids, which were withdrawn after 3 months.

Dr. Kay also described the results of a 1-year RCT of rituximab in 14 scleroderma patients (Rheumatology 2010;49:271-80). Eight patients received rituximab according to the lymphoma regimen (2 cycles of rituximab 375 mg/m^2 IV weekly x 4, at baseline and 24 weeks) plus standard treatment, compared with six who received standard treatment alone. Significant improvements were seen with rituximab in forced vital capacity and diffusing capacity of carbon monoxide. MRSS scores also improved significantly with rituximab, with reductions in collagen deposition in the papillary dermis seen after 6 months.

Dr. Kay is a consultant to Array BioPharma, Bristol-Myers Squibb, Centocor Ortho-Biotech Inc., Eisai Research Institute, Genentech, Johnson & Johnson, Mallinckrodt, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, and UCB. He receives research funding from Roche and Sanofi-Aventis. ■

Bortezomib May Protect Kidneys As Lupus Tx

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – The proteasome inhibitor bortezomib depletes long-lived plasma cells and thus appears to have great potential as an effective treatment for lupus, according to Dr. R. John Looney.

Bortezomib (Velcade) is approved for the treatment of multiple myeloma and mantle cell lymphoma, and in fact has become a very important drug for these conditions. This "real breakthrough drug" has extensive activity against long-lived plasma cells, which in systemic lupus erythematosus – as in myelomas – are believed to produce harmful antibodies, are extremely resistant to existing therapies, and are associated with refractory disease.

The drug has been shown in some "very, very positive" mouse models to protect against nephritis in lupus-like disease, and recent case reports suggest it might do the same in humans, said Dr. Looney, professor of medicine at the University of Rochester, New York.

The cases, which were presented at the 2010 annual European Congress of Rheumatology, demonstrated that intravenous treatment with bortezomib at 1.3 mg/m^2 body surface daily on days 1, 4, and 8, together with 20 mg of dexamethasone orally and repeated one to two times at 21-day intervals, was associated with marked improvements in refractory lupus nephritis patients, he said.

Urine sediments in both patients were inactive at 6 weeks and proteinuria had markedly decreased, reaching normal in one of the patients after 4 months. Furthermore, anti-dsDNA antibodies had markedly decreased within 4 weeks, Dr. Looney said.

The treatment was associated with some minor toxicities. One patient had myalgias, fever, and headache. Also, antibodies to hepatitis B surface antigen and tetanus toxoid decreased, but protective levels were maintained nonetheless.

Providing additional evidence of a potential role for this drug for protecting against renal damage in lupus, studies suggest it is also useful as an antirejection drug in the setting of renal transplant, Dr. Looney said.

Bortezomib has been shown to directly target long-lived plasma cells producing antihuman leukocyte antigen antibodies. Treatment depletes the plasma cells and achieves dramatic reductions in the anti-HLA antibody levels, thereby improving allograft function.

In addition to the interest in the transplant field for using bortezomib as an antirejection drug, it is also likely that this type of drug – a proteasome inhibitor that targets plasma cells – will be among the new agents available for lupus in the coming years, he said.

Dr. Looney disclosed that he has been an adviser for Genentech. ■