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 myogenic leukopenia, 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 extra-cellular matrix proteins by dermal fibroblasts.”

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 tattering scores at 17 different body sites. Over the 1-year 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%).

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

DR. KAY

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-12 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 arterial hypertension died, but this was not believed to be medication related. One patient was repeatedly hospitalized for orthostatic 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 fibrosis such as nephrotic 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 caused 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 and had no effect on oropharyngeal 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.

The 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/m² 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 Bio-Pharma, Bristol-Myers Squibb, Cento- cor Ortho-Biotech Inc., Eisa Research Institute, Johnson & Johnson, Mallinckrodt, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, and UCB. He receives research funding from Roche and Sanofi-Aventis.