Juvenile Scleroderma Affects More Than Just Skin

BY NANCY WALSH
New York Bureau

ABANO TERME, ITALY — Juvenile localized scleroderma—traditionally considered a relatively benign condition with manifestations limited to skin and subcutaneous tissue—is not just simply a skin disease in close to one-quarter of affected children, Dr. Francesco Zulian said at a congress on skin, rheumatism, and autoimmunity.

Investigations of a worldwide database of 727 patients have shown that 22.4% of patients have extracutaneous disease manifestations, said Dr. Zulian of the University of Padua (Italy).

Among patients with extracutaneous manifestations, 66% had the linear subtype of juvenile scleroderma, while 25% had the plaque subtype. An additional 7% had generalized morphea, and 2% had deep morphea. "The mean age of onset was 7 years, but we have 17 patients with onset in the first year of life and 6 with congenital lesions," he said. There was a family history of autoimmune disease in 12%, and a recent history of trauma in 14%. Juvenile localized scleroderma still was not well recognized, and the mean delay in diagnosis was 18 months.

The most common extracutaneous manifestation was arthritis, reported in 12.1%. Neurologic involvement was seen in 4.4%, vascular involvement in 2.4%, and ocular involvement in 2.1%.

The arthritis often is seen on the same side of the body as the cutaneous lesion, which raises the possibility that linear bands of sclerosis spreading across joints could cause inflammation by local mechanisms (Arthritis Rheum. 2005;52:2873-81).

Arthritis, the most common extracutaneous manifestation, was found in 12% of the study patients.

DR. ZULIAN

But the observation that articular involvement sometimes occurred on the opposite side "makes us suspect that some systemic inflammation was going on," Dr. Zulian said.

Neurologic manifestations were seen primarily among children with linear scleroderma of the face. Accordingly, any child with this presentation should be evaluated with an electroencephalogram and CT or MRI, particularly because abnormalities on MRI were found in seven of the children who had no neurologic symptoms, he said.

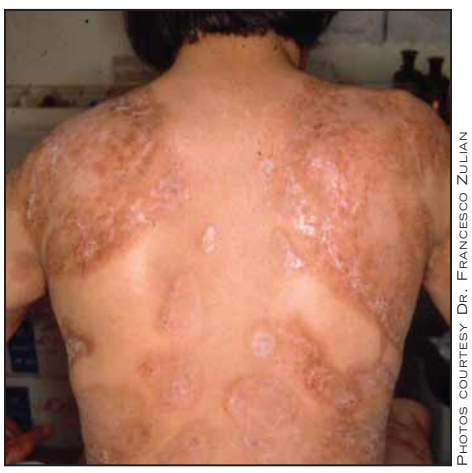
Treatment of the condition was addressed in a separate session by Dr. Davide Meneghesso, one of Dr. Zulian's colleagues at the University of Padua.

"There is no universally accepted treatment," Dr. Meneghesso said. Topical, oral, and parenteral steroids have been used, as has D-penicillamine, vitamin D, and nonsteroidal anti-inflammatory drugs. Various supportive treatments such as anticonvulsants also have been used in patients with extracutaneous complications (Rheumatology 2005 Dec. 20 [Epub ahead of print];doi 10.1093/rheumatology/kei251).

But now, a prospective trial evaluating methotrexate, 15 mg/m^2 per week for 12 months plus corticosteroids, has found that 14 of 27 patients experienced "substantial improvement," Dr. Meneghesso said.

Mean age of the patients was 8.3 years, mean disease duration was 49 months, and the female to male ratio was 2.8:1.0. Nineteen children had linear scleroderma and eight had generalized morphea, he said.

Only two patients did not respond to the treatment. The remaining 11 patients remained stable during 12 months of follow-up, he said. Histologic evaluation in 16 of the patients found improvements in inflammation and fibrosis in nine and stable disease in seven. Side effects were seen in 55% of patients, but none were severe. ■



PHOTOS COURTESY DR. FRANCESCO ZULIAN

Among children with extracutaneous manifestations of scleroderma, the linear subtype (left) was found in two-thirds. Generalized morphea (right) is much more uncommon.

Biologics Offer Profound, Persistent Benefits in Juvenile Arthritis

BY NANCY WALSH
New York Bureau

NEW YORK — Early studies evaluating biologic therapies for juvenile idiopathic arthritis are showing benefits that in many cases are profound and persistent, even among patients with the most severe disease.

These trials also have taught some important lessons about study design, placebo responses, and the importance of correct dosing, according to Dr. Daniel J. Lovell.

In an initial trial investigating etanercept (Enbrel) in 58 patients (mean age 10.5 years) treatment-resistant polyarticular juvenile idiopathic arthritis (JIA) a unique study design was used, Dr. Lovell said at a rheumatology meeting sponsored by New York University.

All patients received a 0.4-mg/kg dose of the drug twice weekly on an open-label basis for 3 months, and those who achieved an American College of Rheumatology pediatric 30 response, which is equivalent to the adult ACR 20 response, were entered into the 4-month double-blind, placebo-controlled phase. As soon as a patient flared he or she could leave the blinded phase and go back on the drug. Flare was defined as a 30% worsening in disease activity.

On average these patients had 25 active joints at baseline; this fell to 4 after 3 months of etanercept, said Dr. Lovell, professor of pediatrics, Cincinnati Children's Hospital Medical Center.

Moreover, only those patients who initially demonstrated a response to etanercept—74% of the cohort—were enrolled in the blinded phase, he said.

Flares typically occurred quickly among patients randomized to placebo, but clinical benefits were regained once the patients restarted etanercept. Some patients have now been followed for 4 years, with persistent benefits in many disease domains. (See chart.) "It's also important to note that on each of these parameters 20%-40% of the population actually normalized, meaning they could have a pain assessment score of zero or no active joints," he said.

Another double-blind study that enrolled 171 patients (mean age 11.4 years) with polyarticular JIA to adalimumab (Humira) at a dose of 24 mg/m^2 body surface area with or without methotrexate is just being completed. There was an initial open phase where all patients received the active drug for 16 weeks.

Among patients receiving adalimumab without background methotrexate, 67% achieved an ACR pediatric 30 response, while 63% and 45% achieved ACR 50 and 70 responses, respectively. Among those with background methotrexate, 88%, 85%, and 69% reached ACR 30, 50, and 70 levels of response, respectively.

"The lesson we can take home as clinicians is that if you're going to use [adalimumab] in patients with juvenile [idiopathic] arthritis it makes sense to combine it with methotrexate," he said. The combination was as safe as adalimumab alone.

Responses were rapid: By week 8 all the patients who were going to respond to the drug had done so.

Another trial that was recently completed evaluated infliximab (Remicade) in doses of 3 mg/kg or 6 mg/kg. This was a more traditional study design, with patients receiving either placebo infusions or infliximab 3 mg/kg at prespecified intervals for 14 weeks. At that time, patients who had been on placebo received infusions of 6 mg/kg of infliximab, while those on the 3 mg/kg regimen continued at that dose.

At week 14, 65% of 122 patients on infliximab had achieved an ACR 30 response, which was the primary end point, as had 48% of those on placebo.

The difference in response rate from placebo for the 3 mg/kg dose, with a *P* value of .051, did not reach statistical significance, so this dose will not be approved by the FDA, Dr. Lovell said.

In the second phase of the trial, however, when patients were receiving infusions of either 3 mg/kg or 6 mg/kg every 8 weeks, approximately 70% of patients in both groups had an ACR 30 response. Among patients receiving the lower dose, 38% developed anti-infliximab antibodies, compared with 12% of those receiving the higher dose. Patients with these antibodies, which develop in response to the mouse component of this chimeric drug, have a three- to fourfold increased risk of having an infusion reaction and also have lower serum concentrations of the drug. ■

Median Disease Activity

	Baseline (N = 58)	Year 1 (N = 52)	Year 2 (N = 47)	Year 3 (N = 41)	Year 4 (N = 32)
Patient assessment of pain (0-10)	3.6	0.3	0.7	0.6	0.9
Patient/parent global assessment (0-10)	5.0	2.0	1.0	1.0	2.0
Physician global assessment (0-10)	6.5	2.0	1.0	1.0	1.0
Total active joints (0-66)	28.5	2.5	3.0	1.5	2.0
Childhood Health Assessment Questionnaire (0-3)	1.4	0.5	0.4	0.4	0.3
C-reactive protein (mg/dL) (normal range 0-0.79 mg/dL)	3.4	0.4	0.1	0.2	0.1

Source: Dr. Lovell

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