

New Raynaud's: Nail Folds Predict Scleroderma

BY KATE JOHNSON
Montreal Bureau

SNOWMASS, COLO — The most significant predictor of progression to scleroderma in a patient with new onset Raynaud's phenomenon is the presence of capillary abnormalities at the proximal nail fold, according to David H. Collier, M.D.

Although scleroderma is primarily managed by rheumatologists, it is dermatolo-

gists who most commonly identify the early skin manifestations of the disorder, said Dr. Collier of the University of Colorado, Denver, and chief of rheumatology at Denver Health Medical Center.

In addition to Raynaud's, these manifestations include skin thickening, ulceration, telangiectases, calcinosis, and pigmentation changes.

Speaking at a clinical dermatology seminar sponsored by Medicis, Dr. Collier explained that Raynaud's phenomenon is

an almost universal component of systemic sclerosis, and yet the vast majority of patients with Raynaud's never progress to scleroderma.

"Up to 10% of adult women can have Raynaud's, and less than 0.1% can go on to develop scleroderma," he said in an interview, adding that about 77% of Raynaud's patients are female.

By examining the periungual area of the finger, under gel with an ophthalmoscope, the physician can easily assess capillary abnormalities at the proximal nail fold, he said.

"Instead of thin little loops of capillaries that you would see in a normal patient, you see capillary dilation and areas that are denuded or dropped out altogether," he said, explaining that capillary dilation occurs early in the disease, and after about 10 years, only denudation is typically visible.

"A patient with abnormal capilloscopy should be followed every 3-6 months for signs of progression to systemic sclerosis," he advised, adding that early identification of scleroderma and referral can allow for a prompt pulmonary evaluation and establishment of gastroesophageal reflux prevention/management.

Pitting or ulceration of the fingertips is another indication that a Raynaud's patient has scleroderma, said Dr. Collier.

"Primary Raynaud's disease does not give you pitting. So if you see pits—especially fingertip pits and ulceration—that's a red light [indicating] that you're dealing with an autoimmune disease. It's almost

always Raynaud's secondary to scleroderma or mixed connective tissue disease, or occasionally lupus," he said.

In addition to the evaluation for capillary abnormalities, the scleroderma work-up for patients presenting with Raynaud's should also include autoantibody testing, he said.

"If they also have the antibodies, that's the subgroup that I worry about the most for progressing to scleroderma, but it's not universal. I've certainly followed people with autoantibodies, and they didn't progress."

Anticentromere antibodies are seen in 20%-30% of scleroderma patients and are the most predictive of risk to progression to limited systemic sclerosis, although they are also commonly seen in primary biliary cirrhosis and, rarely, in other connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, and polymyositis, he said.

Anti-topoisomerase-1 antibodies (e.g., anti-scleroderma [Scl]-70) are present in 9%-20% of scleroderma patients. Anti-RNA polymerase 1-3 antibodies are seen in 20%. Antifibrillar/anti-U3 ribonucleoprotein (anti-U3 RNP) antibodies are seen in 10%, and anti-neutrophilic cytoplasmic antibodies (ANCA) are seen in about 4%, though mostly in patients with diffuse systemic sclerosis. Finally, antipolymyositis/Scl (anti-PM Scl) and anti-Th/To (which recognizes certain RNA processing enzymes) antibodies are seen in about 2% of scleroderma patients. ■

with moderately to severely active rheumatoid arthritis and Crohn's disease treated with REMICADE in clinical trials with a median of 1.1 years of follow-up, 3 patients developed lymphomas, for a rate of 0.07 cases per 100 patient-years of follow-up in patients with rheumatoid arthritis and 0.12 cases per 100 patient-years of follow-up in the combined clinical trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold higher in the RA clinical trial population and 6-fold higher in the overall clinical trial population than expected in an age-, gender-, and race-matched general population based on the Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. An increased rate of lymphoma up to several fold has been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be further increased in patients with more severe disease activity. Other than lymphoma, 13 patients developed malignancies, which was similar in number to what would be expected in the general population. Of these, the most common malignancies were breast, colorectal, and melanoma. (See **WARNINGS, Malignancies**.) Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use. **Patients with Heart Failure** In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction \leq 35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) (see **CONTRAINDICATIONS** and **WARNINGS, Patients with Heart Failure**). **Immunogenicity** Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals $>$ 16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see **ADVERSE REACTIONS, Infusion-related Reactions**) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading. **Hepatotoxicity** Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE (see **WARNINGS, Hepatotoxicity**). Reactivation of hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive) (see **WARNINGS, Hepatotoxicity**). In clinical trials in RA, Crohn's disease and ankylosing spondylitis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls, both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications. ALT elevations \geq 5 times the upper limit of normal were observed in 1% of patients receiving REMICADE. In rheumatoid arthritis clinical trials, 34% of patients who received REMICADE + MTX experienced transient mild ($<$ 2 times the upper limit of normal) or moderate (\geq 2 but $<$ 3 times the upper limit of normal) elevations in ALT compared to 24% of patients treated with placebo + MTX. ALT elevations \geq 3 times the upper limit of normal were observed in 3.9% of patients who received REMICADE + MTX compared with 3.2% of patients who received MTX alone (median follow up approximately 1 year). In Crohn's disease clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced mild to moderate elevations in ALT, compared to 34% of patients treated with placebo-maintenance. ALT elevations \geq 3 times the upper limit of normal were observed in 5.0% of patients who received REMICADE-maintenance compared with 4.0% of patients who received placebo-maintenance. In an ankylosing spondylitis clinical trial in which patients were not receiving MTX, 40% of patients who received REMICADE experienced mild to moderate elevations in ALT compared to 13% of patients treated with placebo. ALT elevations \geq 3 times the upper limit of normal were observed in 12 (6%) REMICADE-treated patients compared to none in placebo-treated patients. **Other Adverse Reactions** Safety data are available from 2629 REMICADE-treated patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 202 with ankylosing spondylitis and 17 with other conditions. Adverse events reported in \geq 5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=350; average weeks of follow-up 59) and REMICADE-treated patients (n=1129; average weeks of follow-up 66), respectively, are: **Gastrointestinal:** Nausea: 20, 21; Abdominal pain: 8, 12; Diarrhea: 12, 12; Dyspepsia: 7, 10. **Respiratory:** Upper respiratory tract infection: 25, 32; Sinusitis: 8, 14; Pharyngitis: 8, 12; Coughing: 8, 12; Bronchitis: 9, 10; Rhinitis: 5, 8; **Skin and appendages disorders:** Rash: 5, 10; Pruritus: 2, 7; **Body as a whole—general disorders:** Fatigue: 7, 9; Pain: 7, 8; **Resistance mechanism disorders:** Fever: 4, 7; Moniliasis: 3, 5; **Central and peripheral nervous system disorders:** Headache: 14, 18; **Musculoskeletal system disorders:** Back pain: 5, 8; Arthralgia: 7, 8; **Urinary system disorders:** Urinary tract infection: 6, 8; **Cardiovascular disorders, general:** Hypertension: 5, 7. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. The most common serious adverse events observed in clinical trials were infections (see **ADVERSE REACTIONS, Infections**). Other serious, medically relevant adverse events \geq 0.2% or clinically significant adverse events by body system were as follows: **Body as a whole:** allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequelae; **Blood:** pancytopenia; **Cardiovascular:** circulatory failure, hypotension, syncope; **Gastrointestinal:** constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia; **Central and Peripheral Nervous:** meningitis, neuritis, peripheral neuropathy, dizziness; **Heart Rate and Rhythm:** arrhythmia, bradycardia, cardiac arrest, tachycardia; **Liver and Biliary:** biliary pain, cholecystitis, cholelithiasis, hepatitis; **Metabolic and Nutritional:** dehydration; **Musculoskeletal:** intervertebral disk herniation, tendon disorder; **Myo-, Endo-, Pericardial, and Coronary Valve:** myocardial infarction; **Platelet, Bleeding, and Clotting:** thrombocytopenia; **Neoplasms:** basal cell, breast, lymphoma; **Psychiatric:** confusion, suicide attempt; **Red Blood Cell:** anemia, hemolytic anemia; **Reproductive:** menstrual irregularity; **Resistance Mechanism:** cellulitis, sepsis, serum sickness; **Respiratory:** adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency; **Skin and Appendages:** increased sweating, ulceration; **Urinary:** renal calculus, renal failure; **Vascular (Extracardiac):** brain infarction, pulmonary embolism, thrombophlebitis; **White Cell and Reticuloendothelial:** leukopenia, lymphadenopathy. The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see **WARNINGS, Hematologic Events**), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see **WARNINGS, Neurologic Events**). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCE:** 1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221-S247.

© Centocor, Inc. 2004
Malvern, PA 19355, USA 1-800-457-6399

License #1242
Revised December 2004 IN04816

A Rare Scleroderma Look-Alike: Nephrogenic Fibrosing Dermopathy

A recently described cutaneous fibrosing disorder could be mistaken for scleroderma, but there are some key differences, said Dr. Collier.

Worldwide, there have been only 170 cases of nephrogenic fibrosing dermopathy (NFD) reported since it was first described in 1997, he said. Yet "I think it's far more common than we're led to believe," he added.

The typical presentation of NFD consists of acute, lumpy, plaquelike indurations involving the lower limbs and occasionally the upper limbs and torso, he said.

Usually, scleroderma starts on the hands and face. But in NFD, these are almost always spared, he said.

The most common distribution of NFD skin presentation is between the ankles and the mid-thighs and between the wrists and mid-upper arms bilaterally, he said. Skin-colored to erythematous papules coalesce into brawny plaques with a peau d'orange appearance. There is a distinctive, ir-



NFD plaques typically take on a peau d'orange appearance.

regular edge with amoeboid projections and islands of sparing within the indurated plaque. Eventually, the skin becomes markedly thickened and woody. Pruritis and causalgia are prominent features.

Unlike scleroderma, NFD often causes severe sharp pains in the affected areas, and renal insufficiency is necessary for the diagnosis.

The biopsy will show deposits of collagen and elastin—spindle cells, dendritic cells, and mucin deposits—“which is different from what we see in scleroderma.”

Although NFD was initially thought to be only a cutaneous disease, there now appears to be a severe myopathic component. Joint contractures may develop within days or weeks of onset, likely resulting from facial and muscle fibrosis, Dr. Collier noted.

The abrupt emergence of this disease suggests that toxic exposures, infectious agents, or medical techniques may be involved.

—Kate Johnson

COURTESY DR. DAVID H. COLLIER