Drugs for Rheumatoid Diseases Trigger Skin Woes

Discontinuing the troublesome medication may not always be possible, necessitating clinical ingenuity.

BY DIANA MAHONEY
New England Bureau

STOWE, VT. — Use of several agents prescribed for the management of arthritis and other diseases seen by rheumatologists can induce cutaneous reactions that require referral to a dermatologist, said Dr. Peter W. Heald at a dermatology conference sponsored by the University of Vermont.

Because these drug-aggravated conditions often present as known diseases but frequently have different underlying mechanisms and treatment responses, diagnosis and management can be problematic, according to Dr. Heald, professor of dermatology at Yale University, New Haven, Conn. Also, the condition the suspect drug is prescribed to treat may make it inadvisable to discontinue the medication. To help unmask some of the dermatologic impostors, Dr. Heald presented a series of clinical cases from his own practice along with management pearls gleaned from personal experience and recent literature.

Interferon-Induced Cytokine Psoriasis

Cytokine psoriasis—a subset of psoriasis with a unique clinical appearance and therapy profile—started appearing with some frequency around 1990, not coincidentally around the time treatment with interferon for hepatitis C became more common, Dr. Heald said. "Over the past decade, we've started seeing tons of patients who are 1-2 months into interferon therapy coming in with psoriasis that's just gone crazy. They have acute, irritated, oozing lesions, sometimes with pruritus and often associated with palmar lesions and acral dermatitis," he said. Of interest, the psoriatic lesions are not local to the interferon injection sites, but rather are all over the body and, if the patient has or is prone to psoriatic arthritis, that will be induced or aggravated as well.

Although the exact underlying mechanism for this is not fully understood, psoriasis is thought to be an immune-mediated disease with a cytokine profile predominantly of the T helper cell, type 1 (TH1) subset. Presumably, interferon-α triggers psoriasis by activating dendritic cells and T cells involved in the pathogenesis of the condition, according to Dr. Heald. "I'm not a big believer in interferon inducing new cases;" it is more likely that interferon causes problems in people who are prone to psoriasis or who have a mild case, he said. "If you've got a condition where you've already got a TH1-mediated process going on in the skin, and you feed that interferon, it's going to cause problems."

The plan for managing this type of psoriasis is to treat the patients while they are completing their course of interferon therapy. "The usual regimen is etanercept—I start them on 50 mg twice a week—with or without prednisone for rapid onset of relief," Dr. Heald said. "In my experience, the response to etanercept for this type of psoriasis is even better than [it is for] regular psoriasis." At the end of the interferon course, patients can be safely tapered off of the etanercept, he said.

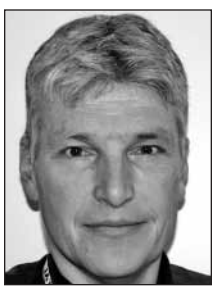
An important consideration in the management of these patients, said Dr. Heald, is to involve the treating physician in the decision process. "Let them know that you are going to start treatment and that you're comfortable using the anti–tumor necrosis factor therapy."

Antimalarial Psoriasis

"I recently saw a patient who started on an antimalarial medication to treat symmetric polyarthritis with psoriasis. Within 2 weeks of starting the drug, he began to develop what I call a 'fill in the gap' type of psoriasis, in which erythema develops in between preexisting plaques," Dr. Heald said. "We've seen a bunch of these cases because for a while at our Veterans [Affairs] hospital a patient had to fail an antimalarial before getting approval for treatment with a biologic for psoriatic arthritis." To manage this condition, "we stop the drug immediately and switch over to something that can treat both [psoriasis and psoriatic arthritis] and possibly a prednisone taper," Dr. Heald said. "I don't think psoriasis patients should ever be put on antimalarials. Hydroxychloroquine inhibits epidermal transglutaminase activity, which leads to irregular keratinization and dermoepidermal detachment and cleft formation. In psoriatics, this leads to an erythrodermic form of the disease."

Efalizumab-Interruption Psoriasis

Most dermatologists have legions of happy psoriasis patients thanks to the efficacy of biologics for continuous control of their conditions, "but there is one little side to this that has not been published enough: the possibility of psoriasis exacerbation when treatment is interrupted," said Dr. Heald, who has had patients weeks and even months into successful therapy whose psoriasis returns with a vengeance following two or three missed doses. "One of my patients went on a trip and forgot his medication for 3 days. He experienced an unbelievably quick, abrupt aggravation with lots of very pruritic new lesions and oozing lesions." It's unclear what's behind this, he said, but it's possible that with an interruption in therapy "all those cells go barreling back into the skin and create this abrupt syndrome."



Lupuslike lesions usually clear 2-3 months after stopping infliximab treatment for RA.

DR. HEALD

To manage the reaction, "I have sometimes tried getting prednisone or cyclosporine in there right away just to get immediate control because these patients get so bad so quickly, and then [I] start another form of therapy."

Interferon: Pyoderma Gangrenosum

Although not common, the development of virulent pyoderma gangrenosum–type ulcers at the interferon injection sites of some patients receiving the drug for multiple sclerosis or hepatitis C, "appears to be the result of interferon aggravating one of the TH1 types of inflammatory processes that typically occurs within 3 months of starting the therapy," Dr. Heald said. Biopsies of the affected areas may show neutrophil infiltrates of vasculitis.

"Because patients and their neurologists love the drug, they're not going to stop it, so they will want you to help manage them through it," Dr. Heald said. This is particularly true for patients with multiple sclerosis. "Patients who are staying on interferon for MS can be taught how to do interlesional triamcinolone injections, which I've had the most success with."

Vitiligo and Imiquimod

Topical imiquimod can induce local interferon-γ release and vitiligo hypopigmentation. "In patients prone to vitiligo, the imiquimod triggers an immunomodulating event that may enhance a latent cell-mediated process," Dr. Heald said. "In the patients I've treated with this condition, nobody has developed vitiligo all over. It's been localized to the area of imiquimod application." Use one of the other topical immunomodulator drugs, he said.

Infliximab and Lupus Erythematosus

Four months on infliximab appears to bring out subclinical lupus in a small percentage of patients with preexisting antinuclear antibodies.

"I've had about a half-dozen patients who are on infliximab for rheumatoid arthritis coming in with a lupus-like syndrome of anular, flat, scaly skin lesions that tend to be mostly on the face and arms," Dr. Heald said.

"The mechanism for the condition is a little bit murky, but what's clear is that in some systems with an ongoing autoimmune process, the anti-TNF action can exacerbate disease," Dr. Heald said. "In these instances, you have to stop the drug. You can't treat through this."

Alternative treatment options include methotrexate or thiopurines. "You want to stay away from the anti-TNF family in general," he said, noting that once infliximab therapy is withdrawn, the skin lesions tend to clear in 2-3 months. ■

Apheresis Healed Refractory Pyoderma Gangrenosum Lesions

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Ulcerated skin lesions in three patients with refractory pyoderma gangrenosum shrank and reepithelialized after 10-11 weekly treatments with granulocyte and monocyte adsorption apheresis, Dr. Mariko Seishima and her associates reported in a poster presentation at the annual meeting of the American Academy of Dermatology.

All three patients were being treated concurrently with prednisolone and cyclosporine, sulfasalazine, or cyclophosphamide, so it's difficult to sort out the exact benefit of granulocyte and monocyte adsorption apheresis (GCAP). It's significant, however, that the lesions had not healed with prior treatment with these medications and others, and clinicians were able to discontinue the drugs or reduce the dosages after GCAP, wrote Dr. Seishima and her associates at Ogaki (Japan) Municipal Hospital.

Pyoderma gangrenosum often is associated with other diseases, including Crohn's disease, ulcerative colitis, or rheumatoid arthritis. One of the three patients treated had rheumatoid arthritis. Recent studies of GCAP for ulcerative colitis have produced impressive results, the investigators noted.

Pyoderma gangrenosum is a chronic skin disorder characterized by intractable ulcers. Histology typically reveals dense cellular infiltration consisting of dominant neutrophils throughout the dermis. After the GCAP treatments, neutrophil counts and leukocyte counts decreased in all patients.

Dr. Seishima and her associates used the column design of GCAP to remove pathogenic granulocytes. The column is a device filled with 220 g of cellulose acetate beads, each 2 mm in diameter. The procedure draws peripheral blood from the cubital vein of one of the patient's arms, perfuses it through the column to remove pathogenic granulocytes, and returns the blood to the cubital vein of the opposite arm. The consecutive weekly sessions each lasted 60 minutes, with a flow rate of 30 mL/min.

No side effects were seen during 8 months of follow-up after completing the GCAP treatments.

For patients with pyoderma gangrenosum who do not respond to treatment with corticosteroids, sulfonamides, and immunosuppressive agents, GCAP may be a useful alternative, according to Dr. Seishima and her colleagues.

A double-blind clinical study is needed to confirm the effects of GCAP, they wrote. Future research also should examine GCAP alone or combined with drug therapy and try to identify the optimal frequency and number of treatments. ■