

When Infections Strike Patients on TNF Inhibitors

BY DOUG BRUNK
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LAS VEGAS — If a patient on a tumor necrosis factor inhibitor such as infliximab or etanercept presents with the signs and symptoms of infection, stop the drug immediately, Dr. Robert Orenstein advised at a dermatology seminar sponsored by the Skin Disease Education Foundation.

"You should do a very aggressive evaluation [because] many of these infections are disseminated at the time they present," said Dr. Orenstein of the divisions of general internal medicine and infectious diseases at Mayo Medical School, Rochester, Minn. "You should start empiric therapy based upon what you think is going on, and you should withhold the agent until the etiology is completed. Don't use these agents if the patient has an active infection."

He discussed his approach to patients on a TNF inhibitor who present with the following infections:

► **Mycobacterial infections.** Obtain a chest x-ray and a purified protein derivative (of tuberculin) skin test. As with AIDS patients, a 5-mm PPD skin test is considered positive.

"You also want to get an excellent his-

tory of exposure, particularly [from] people born in foreign countries or people who are at higher risk because of their profession, before you treat them," Dr. Orenstein said. He noted that the QuantiFERON-TB Gold assay, a commercially available blood test, may be "very helpful" in distinguishing patients with nontuberculous infection from those who are positive for *Mycobacterium tuberculosis*. It takes 24 hours to get the results.

It remains unclear whether treatment of

a latent tuberculosis infection needs to be completed before a patient begins taking a TNF inhibitor. "Most of us would argue that we would like to treat tuberculosis first, and after that use the [TNF] agent. But sometimes that's not a possibility. So in general we would recommend at least 1-2 months of treatment before initiating the biologic agent," he said.

► **Bacterial infections.** The best way to prevent bacterial infections is to make sure these patients get Pneumovax and the in-

fluenza vaccines. Avoid live virus vaccines, he warned. Do not give the yellow fever vaccine to a patient on one of these agents.

► **Viral infections.** Make sure these patients are vaccinated for hepatitis A and B. If a patient on a TNF inhibitor presents with disseminated shingles or disseminated herpes simplex, stop the agent. Treat the patient with aggressive antiviral therapy, he added.

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TNF- α Antagonist Induced Psoriasis Eruption in RA

Anti-tumor necrosis factor- α therapy may not always prevent the new onset or exacerbation of psoriatic skin lesions, according to a case series report involving patients taking the biologics for rheumatoid arthritis.

Infections, β -adrenergic blockers, or lithium were not present in any of the nine patients before the psoriasis erupted, reported Dr. Sonja Kary of Charité University Medicine Berlin, and associates (Arch. Rheum. Dis. [Epub ahead of print], Sept. 8, 2005). The diagnosis of rheumatoid arthritis was definite in all.

HLA typing revealed that one patient had HLA-Cw6, which is linked with psoriasis. Two patients had preexisting, but inactive, psoriasis. Nine patients were treated with adalimumab, etanercept, and infliximab at varying dosages for 4 days to 14 months prior to either new onset (five) or exacerbation (four). Some patients had previously received antimalarials that did not induce psoriasis.

Psoriasis vulgaris was diagnosed in six patients and pustulosis palmoplantaris in three, although pustular symptoms were present in five patients.

Withdrawing or reducing the dose of TNF- α -blocking agents led to improvement in some patients, but this approach was generally limited by the activity of the underlying rheumatoid arthritis. The severity of psoriatic symptoms was reduced when alternative anti-TNF- α agents were used.

—Patrice Wendling

IN PAH, TAKE AIM AT ET-1 THROUGH ET_A SELECTIVITY

Circulating levels of ET-1, the most potent subtype of ET, have been associated with disease severity in PAH.¹ The deleterious effects of elevated ET-1 include cellular proliferation, vasoconstriction, and vascular remodeling.²⁻⁴

In pulmonary arterial hypertension (PAH), endothelin (ET-1) exerts its cardiovascular effects through 2 receptors: ET_A and ET_B. When ET-1 activates the ET_A receptor on the vascular smooth muscle, it leads to vasoconstriction and vascular remodeling.^{4,5} Endothelial ET_B receptors mediate the release of vasodilating nitric oxide (NO) and prostacyclin (PGI₂), while inhibiting and clearing ET-1 from circulation.^{5,6} Blockade of ET_B receptors may significantly impair the balance of endothelium-derived vasodilating substances.^{4,7}

Endothelial dysfunction has been shown to improve with selective ET_A blockade.⁸ Hence, preemptive targeting of ET-1 through selective ET_A receptor antagonism can slow the progression of PAH, and may even provide better overall outcomes.^{2-4,8}

TARGETED ET-1 TREATMENTS MAY PROVIDE BETTER OUTCOMES

Imbalances in the key endothelial cell-derived mediators NO, PGI₂, and specifically ET-1 are thought to be central to the pathogenesis of PAH.⁹ NO and PGI₂ are potent vasodilators with antiproliferative activity.¹⁰ ET-1 is a potent vasoconstrictor with proliferative activity.⁵ Chronically elevated levels of ET-1 are associated with pulmonary vascular resistance, excessive scar formation and cardiac remodeling, cellular proliferation, and cardiac hypertrophy.^{1,11-13}

A reduction of excess ET-1 levels may result in positive outcomes for patients with PAH. It has been shown that in patients with congestive heart failure, elevated ET-1 plasma

Figure 1: ET_A receptor pathway

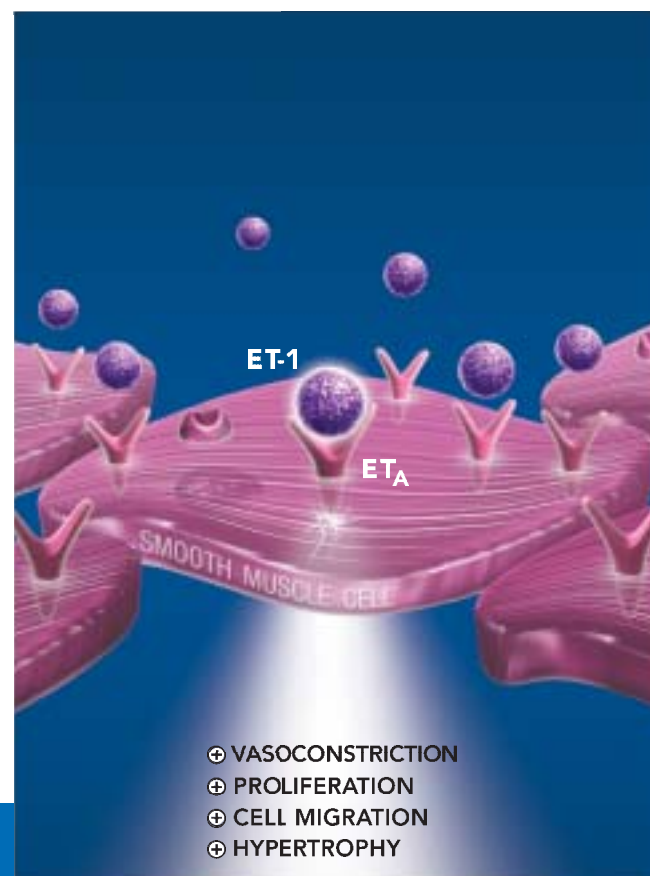


Figure 2: ET_B receptor pathway

