Anti-TNF Therapy May Induce Psoriasis

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF DERMATOLOGY

NEW ORLEANS – Induction or exacerbation of psoriasis is a common and paradoxical side effect of anti–tumor necrosis factor-alpha therapy for rheumatologic and inflammatory bowel diseases.

The paradox lies in the fact that anti-TNF agents are a tremendously effective therapy for moderate to severe psoriasis.

So when a patient with Crohn's disease or rheumatoid arthritis in remission induced by anti-TNF therapy suddenly develops severe psoriasis, it creates a clinical conundrum, observed Dr. Brian F. Mandell at the meeting. Dr. Mandell is a rheumatologist who is professor and chairman of the department of medicine at the Cleveland Clinic.

One striking feature of this anti-TNF-induced cutaneous drug reaction is how long it takes to appear.

DR. MANDELL

Dr. Alice Gottlieb noted that psoriasis induced by TNF blockers is a class effect that, although rare, can be severe and debilitating, especially in cases of palmar-plantar psoriasis.

Unfortunately, palmar-plantar psoriasis is much more common in TNF-blocker-induced/flared psoriasis than it is in the general psoriasis population, Dr. Gottlieb said in an interview.

In his report, Dr. Mandell noted that a strikingly unusual feature of this cutaneous drug reaction is how long it takes to appear. In a recent study by European gastroenterologists and dermatologists, the median interval between the start of infliximab (Remicade) for inflammatory bowel disease (IBD) and the occurrence of psoriasis was 17 months; for adalimumab (Humira), the median interval was 12 months; and with certolizumab (Cimzia), it was 4.5 months, noted Dr. Mandell.

The European study involved 85 patients being treated with anti-TNF agents for Crohn's disease or ulcerative colitis who developed severe skin lesions while their IBD remained quiescent.

Sixty-two patients developed dermatologist-diagnosed psoriasis marked by the classic histologic features, including epidermal hyperplasia, parakeratosis, agranulosis, elongated rete ridges, and dilated dermal capillaries.

Fourteen patients had a history of psoriasis prior to anti-TNF therapy, and another 8 had a family history of the skin disease.

The most frequently affected site was the scalp, in 40 patients. A total of 27 patients had involvement at the axillae, groin, and other flexural sites, which are not typical locations for psoriasis; 21 had both scalp and flexural lesions; and 22 had palmar-plantar psoriasis.

Dr. Mandell's data shed some light on treatments: All 62 patients were promptly placed on topical therapy with corticosteroids, vitamin D analogs, keratolytics, and emollients, with phototherapy being prescribed in selected cases.

Twenty-five patients showed a favorable response, while the remaining 37 had no response at all to topical therapy.

Eighteen patients discontinued anti-TNF therapy altogether, of whom 16 experienced complete regression of their psoriasis. Twenty-six patients switched to a second TNF inhibitor; only 1 showed improvement in skin lesions.

Ten of the 23 patients who developed eczematous lesions had a history of atopy. The median duration of anti-TNF therapy prior to onset of the skin lesions was 11 months for infliximab, 6 months for adalimumab, and 14 months for certolizumab.

The histology was consistent with eczema. The lesions were equally distributed on the scalp, flexural areas, trunk, face, and limbs. Sixteen of 23 patients had a favorable response to topical steroids and emollients. Five pa-

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Important Safety Information About Cymbalta

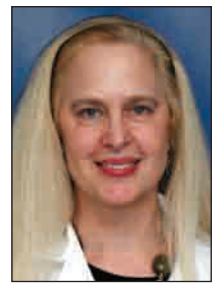
Warning: Suicidality and Antidepressant Drugs—Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients.

Important Safety Information continued on following pages. Brief summary of full Prescribing Information, including Boxed Warning, provided on following pages.

tients were switched to a second anti-TNF biologic, but only one experienced resultant skin improvement. Four patients were eventually taken off anti-TNF therapy altogether, with complete clearing of skin lesions in a median of 3 months.

Dr. Gottlieb, chair of dermatology at the Tufts Medical Center, Boston, noted that the best clinical results are obtained when the TNF blocker is discontinued. Often systemic immunosuppression/immunomodulation is required to control psoriasis induced by a TNF blocker (J. Dermatolog. Treat. 2009;20:100-8).

Altogether, recurrent severe skin lesions caused one-third of IBD patients in this study to discontinue anti-TNF therapy. Extrapolating from the broader Lille University gastroenterology experience, the French investigators estimated that patients on anti-TNF therapy have roughly a 5% risk of developing inflammatory skin lesions, and that the need to halt biologic therapy due to an inability to gain control of the skin eruption is around 1% (Clin. Gastroenterol. Hepatol. 2010;8:1048-55).



Systemic immunosuppression may be needed to control the psoriasis in some patients.

DR. GOTTLIEB

Dr. Mandell said the European report on anti-TNF-treated IBD patients accurately reflects his own experience in using the biologics for rheumatoid arthritis, although he's had more success than the gastroenterologists in switching patients to a different agent within the anti-TNF class in order to continue with treatment.

But he noted that it's necessary to discontinue anti-TNF therapy altogether in a minority of rheumatology patients, and even then the psoriasiform reactions don't always resolve.

Dr. Mandell said he had no relevant commercial interests. Dr. Gottlieb declared financial relationships with the following makers of anti–tumor necrosis factor agents: Abbott, Amgen, Centocor, Pfizer, and UCB. ■

Important Safety Information About Cymbalta *(Cont.)*

Contraindications

- Concomitant use in patients taking Monoamine Oxidase Inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

  At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.
- Cymbalta was associated with an increased risk of mydriasis; therefore, it should not be used in patients with uncontrolled narrow-angle glaucoma and used cautiously in patients with controlled narrow-angle glaucoma.

Warnings and Precautions

- **Clinical Worsening and Suicide Risk**

  All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen, including possibly discontinuing the medication in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If discontinuing treatment, the medication should be tapered. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.**
- Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.
- Because it is possible that Cymbalta and alcohol may interact to cause liver injury or that Cymbalta may aggravate pre-existing liver disease, Cymbalta should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.
- Orthostatic hypotension and syncope have been reported with therapeutic doses of Cymbalta. This tends to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. Consideration should be given to discontinuing Cymbalta in patients who experience symptomatic orthostatic hypotension and/or syncope.
- The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. Concomitant use with serotonin precursors (e.g., tryptophan) is not recommended. Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.
- SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
- On abrupt or tapered discontinuation, spontaneous reports of adverse events, some of which may be serious, have been reported during the marketing of SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.
- Cymbalta should be used cautiously in patients with a history of mania or with a history of a seizure disorder.

(cont.)

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