TNF Blockers Linked to Severe Skin Reactions

Overall, 25% of patients taking the biologics had a dermatologic event compared with 13% of controls.

BY ALICIA AULT
Contributing Writer

Skin reactions to tumor necrosis factor-α–blocking drugs for rheumatoid arthritis might be more common and more varied than previous studies have indicated, results of a new prospective study show.

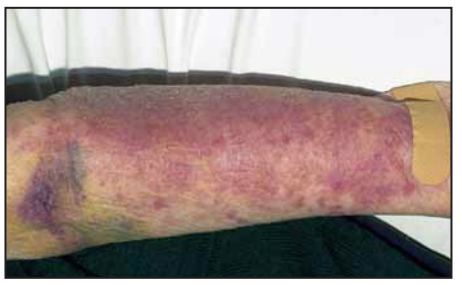
The study authors, led by Marcel Flendrie, M.D., of Radboud University Nijmegen (the Netherlands) Medical Centre, said theirs is the first large prospective study of dermatologic conditions in rheumatoid arthritis (RA) patients taking TNF-α–blocking medications.

Overall, 25% of the 289 patients taking the biologics had a dermatologic event, compared with 13% of the same number of control patients.

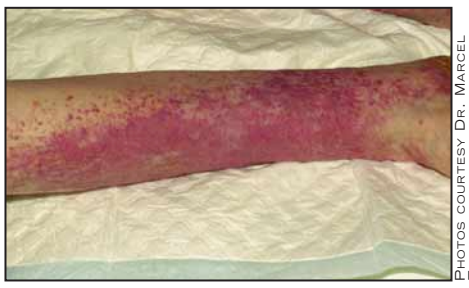
The odds ratio for a patient taking the biologics to require a dermatologic referral was 2.26 (Arthritis Res. Ther. 2005;7:R666-76). The study was published online at BioMed Central's Web site on April 4 (www.arthritis-research.com/content/7/3/r666).

There seemed to be no characteristic at baseline that predicted which patients might be susceptible to a dermatologic event, the authors said.

In the trial, 289 consecutive patients with RA who were started on TNF-α–blocking therapy—infliximab, etanercept, adalimumab, or the experimental agent lenercept—were compared with 289 patients from a cohort of 500 who have been followed at the medical center since 1985 but who had never taken a TNF-α–blocking agent.



An eczematous reaction on the left arm of an RA patient on infliximab is shown.



PHOTOS COURTESY DR. MARCEL FLENDRIE

A similar eruption occurred on the right leg of the same patient.

Any patient who visited a dermatologist during the follow-up period was identified, and any new manifestation or exacerbation of a skin disease or any drug-related eruptions were recorded. The researchers also recorded diagnoses, topical and systemic therapeutic actions, outcome of the event, and any information on rechallenge.

Median follow-up time was 2.3 years. Among the patients taking anti-TNF therapy, 70 (24%) had received more than one agent, 8 (3%) had a history of taking more than two.

Overall, 167 patients were given infliximab, 108 received adalimumab, 78 received etanercept, and 31 were treated with lenercept. In total, there were 128 dermatologic events in the TNF group; 56 events occurred with adalimumab, 49 with infliximab, 16 with etanercept, and 13 with lenercept.

Skin infections accounted for the largest proportion of these therapy-related events, with 33 fungal, bacterial, and viral infections recorded. TNF-α–blocking therapies are known to increase susceptibility to infections, and the study findings suggest that the immunosuppressive agents might also make patients more vulnerable to skin infections, said the authors.

Eczema was diagnosed 20 times in 19 patients, and 3 patients stopped therapy as a result. One patient was hospitalized. The others were treated with topical corticosteroids.

There were frequent cases of drug-related eruptions in the first 5 months, in particular, said the authors.

Most common was a combination of exanthema, urticarial eruptions, lichenoid skin lesions, and purpura. Of 15 patients diagnosed with an eruption, 7 stopped therapy, and 8 continued. One patient was hospitalized.

In smaller numbers, patients also experienced ulcers, benign and malignant skin tumors, vasculitis, actinic keratosis, edema, chronic venous insufficiency/varices, xerosis cutis, and stasis dermatitis.

The occurrence of psoriasiform eruptions in three patients was "particularly interesting," given that etanercept is approved for psoriasis, and infliximab may soon get that approval, the researchers said.

The time between the start of therapy and onset of skin conditions varied, but some events looked more likely to be drug related, including the eruptions, cutaneous vasculitis, a case of systemic lupus erythematosus, dermatomyositis, and a lymphomatoid papulosis-like eruption, the authors continued.

Overall, 19 of the 72 patients who experienced skin problems stopped taking the TNF-α–blocking therapy. ■

Belimumab, Rituximab Are Next in the Biologic Pipeline for RA

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — A host of promising new therapies for rheumatoid arthritis are in development, including the human monoclonal antibody belimumab, Mark C. Genovese, M.D., reported at a symposium sponsored by the American College of Rheumatology.

Belimumab inhibits the activity of B-lymphocyte stimulator (BLyS), a protein that is elevated in the blood and joint fluid of people who have rheumatoid arthritis (RA).

BLyS is believed to contribute to the production of autoantibodies, especially rheumatoid factor, which appears to correlate with disease severity.

An interim analysis of a phase II trial of belimumab (LymphoStat-B) showed a clinical effect at various doses in 283 patients with active moderate to severe RA, said Dr. Genovese, an investigator for Human Genome Sciences, which sponsored the study.

Belimumab also produced statistically significant reductions in all active treatment groups of circulating B cells (CD 20+ and other subsets) and rheumatoid factor, compared with placebo.

"It's an encouraging therapy," Dr. Genovese told this newspaper. "But that enthusiasm has to be tempered by the fact we have to see more studies."

Patients were allowed concurrent standard-of-care therapy, including at least one TNF-α inhibitor and up to 10 mg/day of prednisone.

About 73% of patients were receiving background methotrexate. More than one-third of patients (38%) had been failed by at least one TNF-α inhibitor.

Patients were randomized to receive placebo or belimumab in doses of 1 mg/kg, 4 mg/kg, or 10 mg/kg, given intravenously for 24 weeks.

All patients were dosed on days 0, 14, and 28, then every 28 days for the remainder of the 24 weeks.

The study's primary efficacy end point was the achievement of an American College of Rheumatology (ACR) 20 response at 24 weeks.

Among those in the 1-mg/kg group, 36% achieved an ACR 20 response, as did 17% in the placebo group. This between-group difference was statistically significant.

Trends toward a drug benefit were seen in the 4-mg/kg group (28% ACR 20) and in the 10-mg/kg group (29% ACR 20).

Adverse events were similar across treatment groups, and clinically significant infusion reactions were rare, according to a statement by Human Genome Sciences.

Another promising therapy, rituximab, is a monoclonal antibody that targets CD20 on B cells, said Dr. Genovese, chief of clinical services in the division of immunology and rheumatology at Stanford University, Palo Alto, Calif.

A preliminary analysis of phase III data from the Randomized Evaluation of Long-term Efficacy of Rituximab in RA (REFLEX) trial showed that a greater proportion of rituximab-treated patients achieved an ACR 20 at week 24 than those taking placebo, said Dr. Genovese, also a consultant for Genentech Inc., which sponsored the study.

The study included patients with active RA who had an inadequate response or were intolerant to prior treatment with one or more anti-TNF therapies.

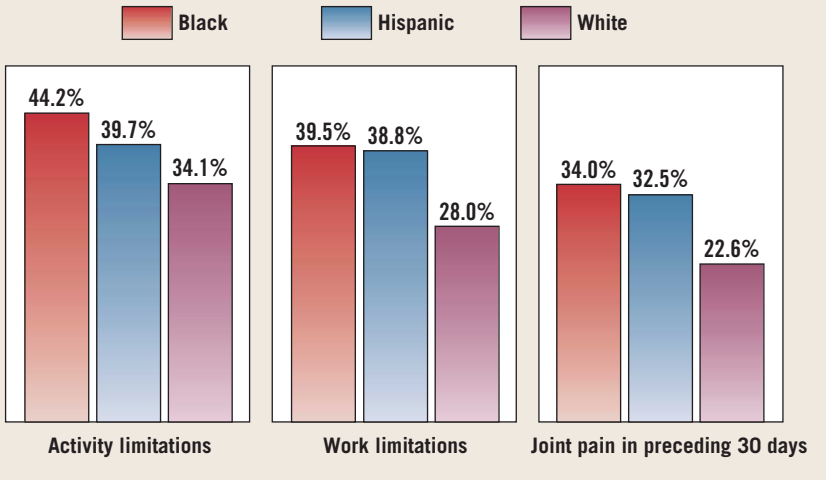
The data did not show anything unexpected regarding safety or efficacy, said Stanley B. Cohen, M.D., the principal investigator for the Radiant Research site of the trial.

The findings so far support the hypothesis that "we have a potential therapy that we can use in patients with disease that is refractory to our most potent therapies to date, which are TNF inhibitors," Dr. Cohen said in an interview.

Detailed results from REFLEX are expected to be presented at the annual congress of the European League Against Rheumatism in June. ■

DATA WATCH

Racial Differences Among Adults Diagnosed With Arthritis



Note: Definition of arthritis includes rheumatoid arthritis, gout, lupus, or fibromyalgia.
Source: 2002 data, Centers for Disease Control and Prevention

KEVIN FOLEY, RESEARCH/ANGIE RIES, DESIGN