Herpes Reactivation Observed With TNF Inhibitors

BY NANCY WALSH
New York Bureau

BARCELONA — The risk of reactivation of herpesvirus infection is increased among patients with rheumatoid arthritis who are treated with the anti–tumor necrosis factor agents, and especially with the monoclonal antibodies infliximab and adalimumab, Dr. Anja Strangfeld said at the annual European Congress of Rheumatology.

"An increased risk of bacterial infections during treatment with the TNF-blocking drugs is well documented, but less attention has been paid to viral infection and reactivation in this regard, so we analyzed data from the German biologics register to ascertain the incidence and risk factors for reactivation of herpesvirus infection," said Dr. Strangfeld, who is an epidemiologist with the German Rheumatism Research Center, Berlin.

Among the patients enrolled in the registry as of June 2006, 1,132 had received etanercept, 563 infliximab, and 1,155 adalimumab.

Among these patients, 160 cases of herpes in 144 patients were reported, with 84 cases being herpes zoster and 76 being herpes simplex, she said.

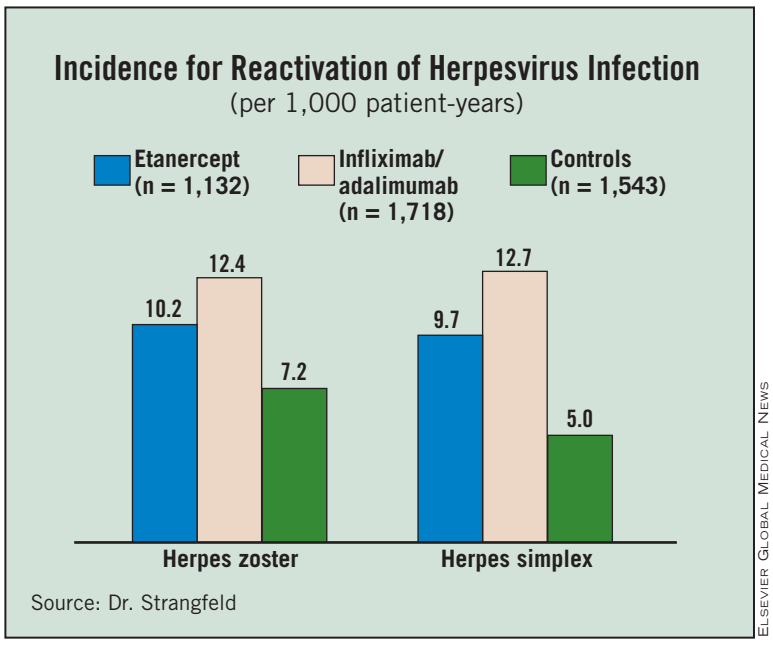
Of note, 15 of the cases of herpes zoster were serious, with 13 being the rare multidermatomal form. An additional two were serious ophthalmic herpes; this results when the virus, which remains latent and lifelong in the sensory ganglia, reactivates in the geniculate ganglion.

The incidence of zoster reactivation among patients being treated with infliximab, adalimumab, and etanercept was compared with rates among control RA patients receiving conventional disease-modifying antirheumatic drugs, and was found to be higher rates among the biologic-treated patients overall. (See box.)

"We also analyzed the rates for the TNF blockers according to their molecular type, because previous analyses of rates of tuberculosis reactivation found differences in rates among patients receiving the monoclonal antibodies infliximab and adalimumab, compared with those receiving the receptor fusion protein etanercept," she said.

Higher rates were seen for the monoclonal antibodies than for etanercept, and particularly for the serious multidermatomal and ophthalmic infections, she noted.

Analysis of risk factors for reactivation identified higher risk for increasing age (hazard ratio 1.24) and for increased duration of disease (HR 1.10).



Elsevier Global Medical News

Drug exposure also influenced risk. Prednisone in daily doses of 10 mg or more was associated with a higher risk (HR 3.53) than were doses less than 5 mg (HR 2.4).

On multivariate analysis, exposure to any TNF blocker was associated with a higher risk (HR 1.77), compared with patients in the control group. A significantly higher twofold risk was seen for infliximab and adalimumab (HR 1.96) but not for etanercept (HR 1.51).

"We therefore concluded that prednisone and anti-TNF use increased the risk for herpes reactivation, and that the risk is higher with treatment with the monoclonal antibodies, which may be due to a different mode of action," she said.

The study was supported by a joint unconditional grant from Wyeth Pharma GmbH, Essex Pharma GmbH, Amgen GmbH, and Abbott GmbH. ■

Tetracycline Eases Cancer Therapy Rash

BY KERRI WACHTER
Senior Writer

CHICAGO — Tetracycline may reduce the severity of rashes associated with epidermal growth factor receptor inhibitors, such as gefitinib and cetuximab, but the antibiotic doesn't seem to prevent such rashes.

More than 75% of patients on epidermal growth factor receptor (EGFR) inhibitors develop an acneiform rash. The rash can be very problematic for patients, said Dr. Aminah Jatoi, a professor of oncology at the Mayo Clinic in Rochester, Minn.

Dr. Jatoi and her colleagues randomized 61 cancer patients to 500 mg oral tetracycline twice daily or placebo twice daily for 1 month. Patients were included if they had started an EGFR inhibitor within 7 days of enrollment and did not have a rash.

"Tetracycline did not prevent EGFR inhibitor–induced rashes. However, diminished rash severity and improved quality of life suggest this antibiotic deserves further study," Dr. Jatoi said at the annual meeting of the American Society of Clinical Oncology.

Rashes were assessed by physicians and patients over an 8-week period. Physicians submitted monthly reports using the Common Terminology Criteria for Adverse Events v3.0. Patients submitted weekly reports, including the answers to a brief questionnaire on rash incidence (the Skindex-16), and an EGFR inhibitor compliance questionnaire.

A small portion of patients—10% in the treatment arm and 17% in the placebo arm—were being treated with gefitinib. An additional 35% and 40% were being treated with cetuximab in the treatment and placebo arms, respectively. The remaining 55% and 43% were taking other EGFR inhibitors (EGFR tyrosine kinase inhibitors) in the treatment and placebo arms, respectively.

Patients are getting a severe rash and it bothers them. Yet at the same time they're saying, 'My tumor may well be responding to this drug.'

"With regard to the primary end point [rash prevention], this was a negative study," Dr. Jatoi said. Physician-reported rash incidence was comparable between the two arms at weeks 4 and 8. At week 4, the incidence was 70% and 76% for the treatment and placebo arms, respectively. Likewise at week 8, the incidence was 87% and 84% for the treatment and placebo arms, respectively. Patient-reported results were similar.

In terms of physician-reported rash severity, significantly fewer patients (17%) on tetracycline had rashes with grade 2 or greater at 4 weeks, compared with those on placebo (55%). However, the difference was not significant at 8 weeks—27% in the tetracycline group vs. 47% in the placebo group. Patient-reported results were similar.

Patients on tetracycline did report less itching on the Skindex-16 starting at week 2, however.

Three patients in each arm stopped taking EGFR inhibitors early because of cancer-related issues. Adverse events were comparable in both treatment arms.

"We invite caution, however, in interpreting these results for two reasons. First, this was a secondary end point not a primary end point. Secondly, the numbers are very small. Dropout rates were quite high over time," Dr. Jatoi said.

The issue of EGFR inhibitor-induced rash is particularly troublesome for patients, because it has been suggested that the presence of skin rash may be associated with tumor response.

"Patients are sometimes finding themselves in quandary. They're getting a severe rash and it bothers them. Yet at the same time they're saying, 'My tumor may well be responding to this drug. I can't stop taking this drug and yet I want to,' " Dr. Jatoi said. ■