No Boost From Infliximab

Prednisone *from page 1*

At that time point, there was no significant difference between the infliximab and placebo groups in proportion of relapse-free subjects, at 43% and 50%, respectively, Dr. Hoffman said.

There also was no difference between groups in the proportion of patients who were able to be tapered to 10 mg of prednisone per day, or in mean cumulative dose of prednisone, which was 3,051 mg in the infliximab group and 3,117 mg in the placebo group.

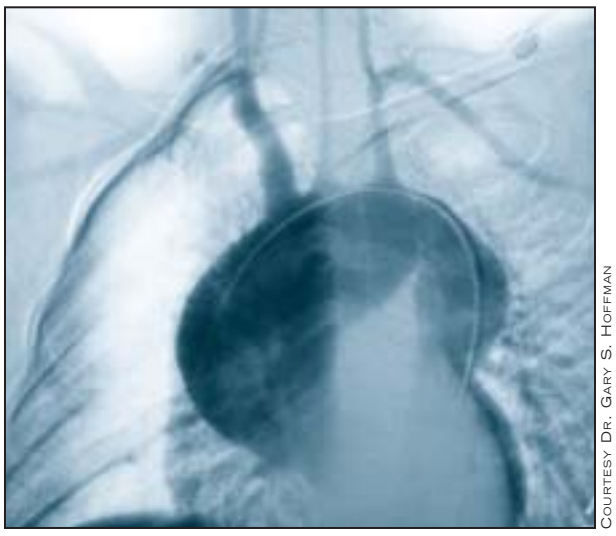
Moreover, there were no differences between days to first relapse, with a median of 97 days in the infliximab group and 85 days in the placebo group.

Accordingly, the study was stopped at 34 weeks rather than at the planned 54-week point, he said.

Safety also was monitored throughout. No severe adverse events were seen, and infections were limited to the upper respiratory tract.

"This experience would lead me to believe that although TNF is found in abundance in the biopsies of patients with GCA, there must be other pathways and mediators that play even more important roles in the pathogenesis," he said.

The study was sponsored by Centocor, and Dr. Hoffman disclosed that he has received research grants and consulting fees from the company. ■



Courtesy Dr. Gary S. Hoffman

Aortic root dilatation and aneurysm formation resulted from giant cell arteritis disease process.

Oral Contraceptives Safe in Women With Stable SLE

BY MARTHA KERR
Contributing Writer

Oral contraceptive use does not increase the number or severity of flares of inactive or mild, stable systemic lupus erythematosus, according to investigators with the Safety of Estrogens in Lupus Erythematosus—National Assessment (SELENA): Oral Contraceptives trial.

Dr. Michelle Petri, of Johns Hopkins University, Baltimore, and her associates randomized 183 women with inactive (76%) or stable active (24%) disease to receive either placebo or an oral contraceptive (OC).

The OC regimen used involved a 35-mcg triphasic ethinyl estradiol plus norethindrone 0.5-1.0 mg for 12 cycles, each 7 days long.

All women used an alternate form of birth control during the study period. The primary end point of the study was a severe lupus flare.

During the first year of follow-up, 7 of the 91 women on OCs (8%) had at least one severe flare of their SLE as did 7 of 92 women (8%) taking placebo.

Rates of severe flare were similar in the two groups, with a rate of 0.084 severe flares per person-year for the study group and 0.087 severe flares per person-year for the placebo group.

Rates of flares per person-year were 1.40 for OC users and 1.44 for placebo patients.

Serious adverse events requiring hospitalization occurred in 15 patients on OCs and 13 placebo patients.

Thrombosis occurred in two OC users and three women on placebo. Two OC users had abnormal liver function tests, and one developed hypertension.

None of these events occurred among women on placebo.

Seven women on OCs had to discontinue treatment, and 12 women on placebo withdrew from the study (N. Engl. J. Med. 2005; 353:2550-8).

In an accompanying editorial, Dr. Bonnie L. Bermas of Brigham and Women's Hospital in Boston commented that the study "supports the use of combined oral contraceptives by those with inactive or moderately active, stable disease. …"

"[T]he option to use combined oral contraceptives in antiphospholipid antibody–negative patients with mild disease appears worth considering in the appropriate clinical setting" (N. Engl. J. Med. 2005;353:2602-4). ■

Etanercept Ups Cancer Risk In Wegener's Granulomatosis

BY NANCY WALSH
New York Bureau

San Diego — Adding etanercept to standard immunosuppressive treatment in Wegener's granulomatosis does not increase efficacy and may increase the risks for developing solid tumors, according to Dr. John H. Stone.

Most patients with Wegener's granulomatosis achieve remission if treated with glucocorticoids and cyclophosphamide, but flares are common, adverse effects are troublesome, and no successful long-term maintenance regimen as yet exists. Moreover, the use of cyclophosphamide carries with it a risk of cancer induction, and patients with this vasculitis already are at elevated risk for malignancy.

During the trial's 25-month follow-up period, there were six solid tumors, all in the etanercept group. None of the patients in the placebo group developed malignancies.

The Wegener's Granulomatosis Etanercept Trial (WGET) was a randomized study comparing standard treatment plus the TNF-α inhibitor etanercept, 25 mg twice weekly, or placebo in 180 patients from eight centers.

Standard treatment in the trial consisted of glucocorticoids plus cyclophosphamide for patients with severe disease, and glucocorticoids plus methotrexate for those with limited disease.

Cyclophosphamide was given in doses of 2 mg/kg per day, adjusted for renal dysfunction. Patients who reached remission in 3-6 months could be switched to methotrexate or, if their creatinine was elevated, to azathioprine, Dr. Stone said.

Methotrexate was given in doses up to 25 mg/week, continued for 12 months after remission was achieved, and then tapered at a rate of 2.5 mg/month.

Azathioprine, used in only a small number of patients, was given in doses of 2 mg/kg per day. This was decreased by 25 mg/month after 12 months of remission.

"There were no differences at all in any of the major efficacy parameters, including sustained remission," Dr. Stone said at the annual meeting of the American College of Rheumatology.

Only 49.4% of patients in the combined groups achieved and maintained disease remission throughout the trial, he said.

But there was one important difference between the etanercept and placebo groups: During the trial's 25-month follow-up period there were six solid malignancies, all in the etanercept group, said Dr. Stone of the Johns Hopkins Vasculitis Center, Baltimore, who chaired WGET.

There were two cases of colon cancer, one breast cancer, on renal cell carcinoma, one cholangiocarcinoma, and one recurrent liposarcoma. All six patients had received cyclophosphamide during the trial, and several had also been treated with this agent previously.

There were no differences between the two treatment groups in terms of gender, disease severity, or history of cancer, though patients in the etanercept group were 4-5 years older at baseline, and less likely to be newly diagnosed with Wegener's granulomatosis.

Data on age- and gender-specific incidence rates for invasive solid malignancies in the Surveillance, Epidemiology, and End Results (SEER) Program suggest that a total of 1.92 solid tumors could be expected in this cohort. The standardized incidence ratio in the trial therefore was 3.12, which was highly statistically significant, he said.

Three additional cancers were seen in the 6 months after the study (N. Engl. J. Med. 2005;352:351-61). One was prostate cancer in a 70-year-old man in the etanercept group; he had not received any cyclophosphamide during the trial. A second was in a patient initially randomized to placebo, who dropped out after a second severe flare. This patient was subsequently treated with infliximab for 14 months and was diagnosed with disseminated renal cell carcinoma.

The third was a cholangiocarcinoma in a patient in the placebo group who had not received any cyclophosphamide during the trial.

There were no differences between the groups in terms of the percentage of patients who had received cyclophosphamide before the trial, who had ever used daily cyclophosphamide, in the mean duration of daily cyclophosphamide therapy, or in the maximum daily cyclophosphamide dose.

"All of this does not prove an association between TNF inhibition, cyclophosphamide, and malignancy. But there is a biologic plausibility for this association—[the abbreviation] TNF stands for tumor necrosis factor," Dr. Stone said.

Like infliximab and adalimumab, etanercept blocks this cytokine, which was shown in the 1970s to lyse tumors in vitro and in mice.

In discussing his findings, Dr. Stone noted that a strength of the study was the fact that the malignancy data were completely unbiased and were only detected at the end of the trial, when the database was unlocked.

Also important was the fact that the data were collected in the context of a clinical trial. "We know that postmarketing studies are very good at detecting rare events but not so good at detecting events that are common. Most of these cancers, such as those of the colon and breast, are common, so the likelihood of detecting them in any setting other than a clinical trial would be quite small," he said.

The lack of efficacy and the heightened risk of malignancy seen in the trial also have potential implications for the use of other TNF blocking agents in Wegener's granulomatosis; in rheumatoid vasculitis, where patients might have received etanercept previously and now require cyclophosphamide; and in patients with systemic lupus erythematosus, many of whom have been previously treated with cyclophosphamide and now may be being given an anti-TNF drug, he said.

Ongoing follow-up from WGET, which was funded by the National Institutes of Health, the Food and Drug Administration Office of Orphan Products, and Amgen, is underway. Dr. Stone stated that he had no financial conflicts to disclose. ■