Natalizumab Cuts Hospitalization Rates in Crohn's

BY HEIDI SPLETE
Senior Writer

SAN DIEGO — Treatment with natalizumab significantly reduced the rates of overall hospitalization and disease-specific hospitalization for adults with Crohn's disease, according to data from 1,373 adults presented at the annual Digestive Disease Week.

Hospitalization is one of the greatest expenses associated with Crohn's disease (CD), and preventing hospitalization remains a major goal of treatment, said Dr. Bruce E. Sands, a gastroenterologist at Massachusetts General Hospital and Harvard Medical School, both in Boston.

To investigate the impact of natalizumab on all-cause and CD-specific hospitalizations, Dr. Sands and his colleagues analyzed pooled data from two previous randomized, controlled trials—ENCORE (Evaluation of Nifedipine and Cerivastatin on the Recovery of Endothelial Function) and ENACT-1 (Evaluation of Natalizumab as Continuous Therapy)—which included a total intent-to-treat population of 1,414 persons.

The two patient groups had an average age of 38 years and similar demographic characteristics at baseline. The patients had been randomly assigned to receive an intravenous dose of 300 mg natalizumab or a placebo every 4 weeks for a 12-week induction period. The hospitalization rate was calculated as hospital admissions per 100 courses (per 100 patients). The study involved an additional analysis of a subgroup of 346 patients who had failed prior anti-TNF therapy and had active inflammation, as shown by elevated C-reactive protein levels. "We observed a total of 136 all-cause hospitalizations in the entire cohort, and of these, 109 were Crohn's related," Dr. Sands said.

In a multivariate analysis, natalizumab was associated with a significant reduction of 35% in the all-cause hospitalization rate. Natalizumab use also was associated with a comparable 30% reduction in the CD-related hospitalization rate, but the difference was not statistically significant.

In the multivariate model, the effect size was even more dramatic for the subset of anti–TNF-resistant patients. The all-cause hospitalization rate in this group was significantly lower for patients who received natalizumab, compared with placebo (9.7/100 patients vs. 20.8/100 patients). The CD-related hospitalization rates also were significantly lower for natalizumab patients vs. placebo patients (6.3/100 patients vs. 12.8/100 patients). "Both anti-TNF experience and elevated C-reactive protein were associated with greater risk of hospitalization," he added.

In both univariate and multivariate analysis, the other independent predictors of hospitalization were low body mass index, baseline C-reactive protein level, prior anti-TNF experience, and elevation of baseline Crohn's Disease Activity Index (CDAI). Age, gender, and baseline steroid and immunosuppressant use were not associated with risk of hospitalization.

Dr. Sands has received consulting fees, grants, and research support from companies including Abbott Laboratories, Centocor Inc., Genentech Inc., Procter & Gamble Pharmaceuticals Inc., Otsuka America Pharmaceutical Inc., Shire PLC, and UCB BioPharma. ■

Methotrexate Failed to Boost Infliximab's Benefit in Crohn's

BY ALICIA AULT
Associate Editor, Practice Trends

SAN DIEGO — Adding methotrexate to infliximab was not superior to infliximab alone in Crohn's disease, according to a presentation at Digestive Disease Week.

Both drugs are effective on their own, but it was not known whether a combination approach would be more effective, said Dr. Brian Feagan, professor of medicine and professor of epidemiology and biostatistics at the University of Western Ontario, London, and director of Robarts Research Institute.

Dr. Feagan and his colleagues at 15 Canadian centers conducted a 50-week, double-blind, placebo-controlled parallel-design trial. All patients had active Crohn's disease and were randomly assigned to receive methotrexate or placebo in addition to infliximab. There were 63 patients in each group.

Both groups received intravenous infliximab at 5 mg/kg at weeks 1, 3, and 7 as well as every 8 weeks thereafter. All patients received intravenous infusions of hydrocortisone (200 mg) before infliximab.

The methotrexate group received 10 mg in week 1, 10 mg in week 2, and then 20 mg for 2 weeks, followed by 25 mg each week for the duration of the trial. Every patient received prednisone induction therapy within 6 weeks of the trial's start. Tapering of prednisone began at the study's start in a manner that ensured that all patients had discontinued by week 14.

The primary outcome was time to treatment failure, strictly defined as failure to enter prednisone-free remission at week 14 and failure to maintain remission through week 50. The analysis consisted of a survival analysis based on a log rank test for the primary analysis.

About half of the 126 patients completed to week 50. Overall, the patients were somewhat older than those who normally participate in induction studies, said Dr. Feagan, noting that the average age was 40 years. Also, the proportion of smokers was large—about 40%. The average score on the Crohn's Disease Activity Index (CDAI) was 210, despite the fact that patients were taking an average of 30 mg prednisone daily. One-quarter had received antimetabolite therapy in the past.

Overall, there was no difference between the methotrexate group and the placebo group. The induction success rate was high in both groups—76% for the methotrexate arm, and 78% for the placebo arm. At week 50, 56% of methotrexate patients and 57% of placebo patients had steroid-free remission.

There was a very high response rate—87% in both groups—in patients who had Crohn's for less than 2 years. For long-established disease, the response rate was lower, at 40% for both groups, he said.

The quality of life at the end of the study was very high—almost normal—for both groups, and there were no differences between the two arms in CDAI scores. The combination therapy was well tolerated, with slightly fewer in the methotrexate group having infections (59%, or 37 patients), compared with the placebo group (62%, or 39 patients).

There were 22 patients who had a serious adverse event in the methotrexate arm, compared to 11 for the placebo group, with the primary difference being an exacerbation of Crohn's.

Dr. Feagan concluded that the study showed a high degree of success in induction and maintenance of remission over 1 year in both treatment groups. The results mean that "our best inductive regimen is highly effective," he said.

The study gives "a very clear message," and that is, "if you're going to achieve very high rates of steroid-free remission in the long term you need to use both of our best agents together and you need to treat early," Dr. Feagan said.

Dr. Feagan reported that he is a consultant for Centocor Inc., which makes and sells infliximab. ■

Older Age Is a Strong Predictor of Early Mortality After GI Bleeding

BY HEIDI SPLETE
Senior Writer

SAN DIEGO — Older age was the strongest predictor of early mortality in adults with gastrointestinal bleeding after investigators controlled for medications and comorbidities, according to data from more than 1,000 adults treated at a single medical center.

More clinicians have turned to low-dose aspirin and antithrombotic agents for cardiovascular disease prevention, but the interaction of these products with other risk factors for GI bleeding has not been studied thoroughly.

"We aimed to assess the 30-day mortality after upper gastrointestinal bleeding in association with the use of NSAIDs, low-dose aspirin, and other antithrombotic drugs," Dr. Ali S. Taha of Crosshouse Hospital and the University of Glasgow, Scotland, and associates wrote in a poster presented at the annual Digestive Disease Week.

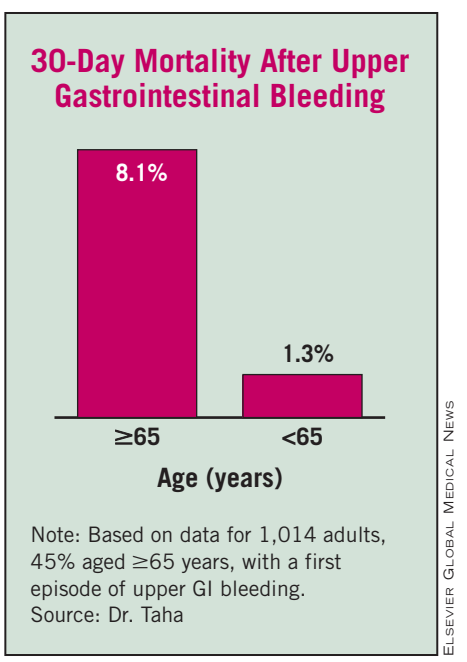
The investigators analyzed data from 1,014 adults who presented with a first episode of upper GI bleeding. A total of 45% of the patients were aged 65 years and older, and 8.1% of these patients died within 30 days of bleeding, compared with 1.3% of the younger patients.

After adjustment for multiple variables, patients aged 65 years and older had a significantly greater risk of 30-day mortality compared with their younger counterparts. In a univariate analysis, cerebrovascular disease, cardiovascular disease, and the use of diuretics, digoxin, and either low-dose aspirin or other antithrombotic drugs were significantly associated with an increased risk of 30-day mortality. Low-dose aspirin was defined as 75 mg/day, and the antithrombotic drugs included clopidogrel, dipyridamole, and warfarin.

Use of NSAIDs had no significant impact on 30-day mortality, and the specific withdrawal of rofecoxib (Vioxx) had no apparent effect on 30-day mortality rates in this population. The Blatchford score (an accepted measure of risk in patients with upper GI bleeding) was calculated using both clinical and laboratory data at each patient's presentation. Patients scoring higher than 10 on this measure had five times the risk of early death, compared with patients scoring 0-2.

Despite the importance of comorbidities and medication use, the results suggest that age is a strong and independent predictor of early mortality in patients with upper GI bleeding. More studies are needed to determine the clinical implications for treatment, Dr. Taha said in an interview. "Ulcer prevention should be considered seriously in elderly patients, particularly in the presence of other comorbid conditions and use of ulcerogenic drugs. And once bleeding has taken place, such patients should be targeted for intensive management."

Dr. Taha said he has received grants and research support from Astellas Pharma Inc., AstraZeneca Pharmaceuticals, Merck & Co., and Yamanouchi Pharmaceutical Co. ■



Pages 32a—32b