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

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 Roberts 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 methotrexate 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 had prednisone tapering 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 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 larger—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 46% 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 (9%, or 37 patients), compared with the placebo group (64%, or 19 patients).

There were 22 patients who had a serious adverse event in the methotrexate arm, compared to 11 for the placebo arm, 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 induc tive 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

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 a study presented at the annual Digestive Disease Week.

More clinicians have turned to low-dose aspirin and antiplatelet 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 antiplatelet drugs,” said 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 antiplatelet drugs were significantly associated with an increased risk of 30-day mortality. Low-dose aspirin was defined as 75 mg/day, and the antiplatelet 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.

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. “Upper 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 AstraZeneca Pharmaceuticals, Merck & Co., and Yamanouchi Pharmaceutical Co.