Digestive Disease Week and American Diabetes Association

Walter Alexander

Digestive Disease Week

From May 17 to 22, 2008, in San Diego, Digestive Disease Week covered the latest advances in gastroenterology, hepatology, endoscopy, and surgery as well as the prevention, diagnosis, and treatment of digestive disorders. The meeting attracted thousands of physicians, researchers, and academics. The first portion of this month's column addresses ulcerative colitis and Crohn's disease.

ULCERATIVE COLITIS

Balsalazide (Colazal)

- Brian Bosworth, MD, Assistant Professor of Medicine, Weill-Cornell Medical College of Cornell University, New York, New York

A twice-daily formulation of balsalazide tablets (Colazal, Salix) improved signs and symptoms of mild-to-moderate ulcerative colitis, according to phase 3 clinical trial results presented by Dr. Bosworth. The reduced-dosing regimen, he stated, "has the potential for higher compliance with self-administered treatment." Poor compliance with the currently approved formulation of three doses per day, he added, is a major problem for these patients.

Dr. Bosworth and co-investigators for the double-blind, placebo-controlled, multicenter trial enrolled 249 adults with symptoms of mild-to-moderate active ulcerative colitis with Modified Mayo Disease Activity Index (MMDAI) scores of 6 to 10 at baseline. Subjects had subscale ratings of 2 or higher for both rectal bleeding and mucosal appearance.

Patients were randomly assigned to three 1,100-mg balsalazide tablets (n = 166) twice daily or three matching placebo tablets (n = 83) twice daily for eight weeks. Colonoscopy or sigmoidoscopy screening was conducted up to seven days before randomization and at the study's end.

Dr. Bosworth reported benefits for the balsalazide group across a wide range of endpoints. A significantly larger proportion of balsalazide patients achieved improvements in total MMDAI scores at the end of the study (67% vs. 47%, respectively; $P = 0.004$), and mean decreases in total MMDAI scores from baseline to week eight were significantly larger with balsalazide than with placebo (-3.4 ± 3.0 vs. -2.3 ± 3.0; $P = 0.002$).

Benefits among the balsalazide subjects, compared with the patients receiving placebo, were also reported for rectal bleeding (59% vs. 42%, respectively; $P = 0.01$); Physician Global Assessment (PGA) scores (60% vs. 36%; $P = 0.0004$); mucosal appearance (53% vs. 37%; $P = 0.02$); and improvements in bowel frequency (49% vs. 37%; $P = 0.08$).

Dr. Bosworth concluded: "As assessed by the MMDAI, balsalazide tablets, administered as 3.3 g twice daily, are effective in improving the signs and symptoms of mild-to-moderate ulcerative colitis. This new tablet formulation reduces both pill and dosing burden in patients with active ulcerative colitis and may improve patient compliance."

Infliximab (Remicade)

- William J. Sandborn, MD, Mayo Clinic, Rochester, Minn.

An analysis of data from a clinical trial of infliximab (Remicade, Centocor) for ulcerative colitis demonstrated that substantial proportions of patients who do not respond to the agent following the first dose might ultimately respond to a second or third dose.

In the large phase 3 registration trials of infliximab (Active Ulcerative Colitis Trials 1 and 2 [ACT 1 and ACT 2]), Dr. Sandborn stated, approximately two-thirds of patients responded to infliximab at the eighth week after three induction doses (5 or 10 mg/kg) given at weeks zero (baseline), two, and six. One-third of the placebo patients responded in the same period. The objective of the current analysis of efficacy data from ACT 1 and ACT 2 was to determine, among patients not responding to their first or second induction infliximab dose, what proportion responded after the second and third induction doses.

ACT 1 and ACT 2 each included 364 patients with active ulcerative colitis despite the use of corticosteroids, azathioprine (Azasan, Salix), and 6-mercaptopurine (6-MP) (Purinethol, Gate). All of the patients had endoscopic evidence of moderate or severe ulcerative colitis with endoscopy scores of 2 or above and total MMDAI scores of 6 to 12 inclusive. They had been randomly assigned to receive placebo (n = 242) or infliximab 5 or 10 mg/kg at weeks zero, two, and six and every eight weeks through week 46 in ACT 1 and through week 22 in ACT 2. The primary endpoint of clinical response was determined from the MMDAI score, which comprised stool frequency, rectal bleeding, PGA scores, and endoscopy findings.

Using PGA subscores, Dr. Sandborn reported that about 50% of patients with moderate or severe disease at week zero had mild or no disease after their initial infliximab infusion; 247 patients had not responded by the second week. Among these, about one-third responded at week six following their second dose of infliximab. Of 169 patients who had not responded by week six after two doses, more than a fourth responded at week eight after receiving a third dose. By week eight, about 74% of the 464 infliximab-treated patients ultimately achieved

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a PGA response. Looking at patients with a PGA response according to baseline levels of C-reactive protein (CRP) (1 or higher, elevated, or less than 1) revealed no differences in 70% and 76% of patients, respectively. Adverse events were similar in all groups.

"The results of these analyses," Dr. Sandborn said, "demonstrate the incremental benefit of a second and third infusion of infliximab in patients with moderately or severely active ulcerative colitis."

CROHN'S DISEASE

Infliximab and Methotrexate

- Brian Feagan, MD, Robarts Research Institute, London, Ontario, Canada
- Gary Lichtenstein, MD, Director, Center for Inflammatory Bowel Disease, and Professor of Medicine, University of Pennsylvania, Philadelphia, Pa.

In patients with active Crohn's disease, adding methotrexate to infliximab (Remicade) conferred no added benefit. According to results of a 50-week, double-blind, multicenter, controlled trial, Dr. Feagan noted that although the patients requiring corticosteroid therapy have a poor prognosis, the best monotherapy rates for inducing and maintaining prednisone-free remission over a year are about 25%. Based on experience in rheumatoid arthritis, he said, combination therapy is the logical next step.

Setting out to compare the efficacy and safety of combined infliximab and methotrexate with infliximab plus placebo, investigators enrolled 126 patients receiving induction therapy with prednisone 15 to 40 mg daily. The mean age of the patients (56% were men) was 39 years. Methotrexate 25 mg was given subcutaneously (SQ) weekly, and infliximab 5 mg/kg was given intravenously (IV) at weeks one, three, seven, and every eight weeks thereafter. Investigators evaluated disease activity using the Crohn's Disease Activity Index (CDAI); global ratings; quality of life using the 36-item Short-Form Survey (SF-36); and CRP, an indicator of active inflammation; safety; and tolerability.

Three criteria defined treatment success: a score of below 150 on the CDAI, no clinical need for prednisone supplements at week 14, and no relapse though week 50. A second primary endpoint was time to treatment failure.

At week 14, treatment induction success rates were very high in both groups: 76.2% with infliximab/methotrexate and 77.8% with infliximab/placebo. At week 50, rates were 55.6% and 57.1%, respectively. Differences were not significant at either time interval.

As for disease duration, an 80% success rate was noted for both groups at 50 weeks among patients with disease lasting less than two years, compared with 40% for disease lasting more than 12 years. Treatment success in patients with CRP levels below 4 mg/L was also similar in both groups. CDAI scores did not differ, but they trended in favor of infliximab alone ($P = 0.09$). Mean SF-36 scores were nearly identical at week 14 (46.6 for infliximab/methotrexate; 47.6 for infliximab alone).

Maintenance therapy with infliximab plus methotrexate, Dr. Feagan noted, was well tolerated, although the combination was not more effective than infliximab maintenance therapy. He noted a high degree of success with both regimens.

Dr. Lichtenstein commented in an interview, "By adding a drug such as methotrexate or steroids, you are just increasing the risk of serious adverse events."

Certolizumab Pegol (Cimzia)

- Severine Vermeire, MD, University Hospital Gasthuisberg, Leuven, Belgium

For patients in whom infliximab treatment failed because of loss of response or intolerance, certolizumab pegol (Cimzia, UCB Group) was efficacious in the 26-week open-label WELCOME trial, according to Dr. Vermeire. This pegylated humanized Fab′ fragment binds tumor necrosis factor-alpha (TNF-).

The trial's aim was to assess the efficacy and safety of certolizumab pegol 400 mg SQ every two weeks for the induction of clinical response and remission in patients with moderate-to-severe Crohn's disease and a well-defined treatment failure with infliximab. Loss of infliximab response was defined as a CDAI score of more than150 points and a minimum increase of 70 points in the CDAI score at two consecutive visits, compared with the CDAI score at week six, Dr. Vermeire said.

Acute infusion reactions to infliximab included one or more of the following during or within two hours of administration: hypotension, urticaria, flushing, facial or hand edema, throat tightness, oral cavity or lip edema, headache, or shortness of breath. Delayed reactions included rash, fever, polyarthralgia, or myalgias. The primary endpoint of the trial was response rate at week six.

Enrolled patients (N = 539) were adults with a mean age of 35.9 years; 64% were female. Baseline CDAI scores ranged between 220 and 450. About 56% of patients had experienced loss of response only, 37% had hypersensitivity to infliximab only, and 6% had both. Eligible concomitant medications for Crohn's disease included 5-acetylsalicylic acid (ASA); antibiotics; corticosteroids at a stable dose for two weeks; azathioprine; 6-MP; or methotrexate at a stable dose for eight weeks. Subjects were expected to remain on stable doses of these medications except for the corticosteroids, which could be tapered off after the eighth week.

Clinical responses, consisting of a 100-point decrease in CDAI scores at week six and over the induction period, were reported in 61% of patients, and 68% of patients experienced a 70-point reduction. Analyses of concomitant medications, baseline CDAI scores, and reasons for stopping infliximab showed no differences among subgroups. Adverse events led to discontinuation of certolizumab pegol in 6.5% of patients.

Dr. Vermeire concluded, "Certolizumab pegol 400 mg subcutaneously is an efficacious treatment for rapidly inducing response and remission in patients with moderate-to-severe Crohn's disease for whom infliximab treatment has failed."

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American Diabetes Association, 2008 68th Annual Scientific Session

This year's meeting of the ADA in San Francisco saw a record-breaking total of 21,000 attendees. Two clinical trials, ACCORD and VADT, which were designed to see whether intensive treatment to lower blood glucose improved outcomes, are discussed. Also covered in this article is a trial of sitagliptin plus metformin for lowering blood glucose.

Action to Control Cardiovascular Risk (ACCORD) Trial

- John B. Buse, MD, PhD, CDE, Associate Professor; Director, Diabetes Care Center; and Chief, Division of General Medicine and Clinical Epidemiology, University of North Carolina School of Medicine in Chapel Hill, N.C.
- Hertzel C. Gerstein, MD, McMaster University and Hamilton Health Services, Ontario, Canada
- Denise G. Simons-Morton, MD, PhD, National Institutes of Health, Bethesda, Md.

At the forefront of the meeting's discussion of ACCORD, findings revealed that treating patients to achieve lower glycosylated hemoglobin (HbA_{1c}) goals, long considered a sure benefit, can entail serious risks. In a two-hour review of this trial, Steering Committee Vice-Chair Dr. Buse noted that in January 2008, the decision was made to discontinue the intensive-glycemia-treatment arm. ACCORD investigators had sought to determine whether rates of cardiovascular disease (CVD) events could be reduced in diabetic patients by intensively targeting three important risk factors for CVD: hyperglycemia, dyslipidemia, and hypertension. The specific question to be answered was whether a therapeutic strategy aimed at reducing the glycosylated hemoglobin count (HbA_{1c}) to below 6% would decrease rates of CVD events more than a strategy targeting a count of between 7% and 7.9% (with the expectation of achieving a median of 7.5%) in middle-aged and older type-2 diabetic patients at high risk for a CVD event.

The controlled, 2-by-2 factorial multicenter trial randomized 5,128 patients to treatment aimed at achieving intensive glycemic control (HbA_{1c} of below 6%) and 5,123 patients to standard glycemic control (HbA_{1c} of 7% to 7.9%). To be eligible for enrollment, patients had to meet the following criteria:

- stable type-2 diabetes for three months or more
- HbA_{1c} levels between 7.5% and 9% (with more medications) or 11% or below (with fewer medications)
- 40 to 79 years of age with previous CVD events or 55 to 79 years of age with anatomical atherosclerotic CVD
- albuminuria
- left ventricular hypertrophy or one or more CVD risk factors
- a body mass index (BMI) of 45 kg/m^2 or below
- a creatinine level of 1.5 mg/dL or less

The primary outcome was a first occurrence of nonfatal myocardial infarction (MI) or nonfatal stroke or CV death.

The antihyperglycemic formulary in ACCORD included metformin (Glucophage, Bristol-Myers Squibb), rosiglitazone (Avandia, GlaxoSmithKline), glimepiride (Amaryl, Sanofi-Aventis), repaglinide (Prandin, Novo Nordisk), acarbose (Precose, Bayer), insulin glargine (Lantus, Aventis), insulin aspart (NovoLog, Novo Nordisk), 70/30 N, R insulin (Lilly), and exenatide (Byetta, Amylin/Lilly). Compared with the standard-therapy group, the intensive-therapy group had a lower HbA_{1c} goal, more physician visits (every one to two months plus at least one interim call), point-of-care HbA_{1c} assessments, greater use of multiple medications, and greater use of insulin.

Analysis of these results, presented by Dr. Gerstein, showed that the intensive glycemia-lowering strategy was associated with more weight gain; significantly higher rates of hypoglycemia requiring any type of assistance (16.2% receiving intensive therapy, 5.1% receiving standard therapy, $P < 0.001$); or significantly higher rates of hypoglycemia requiring medical assistance (10.5% vs. 3.5%; $P < 0.001$), with hypoglycemia episodes occurring in a larger number of participants.

All-cause mortality was higher by 22% in the intensive-treatment group (1.41% per year vs. 1.14% per year; hazard ratio [HR] = 1.22; $P = 0.04$). The primary outcome was reported at 6.86% in the intensive group and in 7.23% in the standard group ($P = 0.16$).

Among secondary endpoints, significantly more frequent in the intensive-treatment group were mortality (5.01% vs. 3.96%, respectively; $P = 0.04$), and death from CVD (2.63% vs. 1.83%; $P = 0.02$). However, the number of nonfatal MIs was lower in the intensive group than in the standard-treatment group (3.63% vs. 4.59%; $P = 0.004$).

Dr. Gerstein concluded that in this population, a therapeutic strategy that targets HbA_{1c} levels below 6%, compared with levels of 7 to 7.9%, increased mortality over 3.5 years.

"There is no significant effect of the glycemic intervention on the primary outcome at this time," he said.

Final ACCORD results are expected to be published in late 2010.

Summarizing the overall findings, Dr. Simons said that ACCORD identified a previously unknown harm of intensive glucose lowering in high-risk individuals with type-2 diabetes. She underscored that ACCORD was designed to test a therapeutic strategy, not specific components of the strategy. Numerous factors, she added, differed between the randomized groups.

Veterans Affairs Diabetes Trial (VADT)

- William C. Duckworth, MD, Veterans Diabetes Trial Co-Chair and Professor of Clinical Medicine, University of Arizona, Phoenix, Ariz.
- Carlos Abraira, MD, VADT Co-Chair and Professor of Medicine, Miami Veterans Affairs Medical Center, Miami, Fla.

VADT was the second major study to suggest that intensive glucose lowering entailed significant risks. The aim of the

7.5-year study was to examine a typical older population of veterans, mostly men, who were approximately 60 years of age at the outset. All patients had failed to respond to what Dr. Duckworth called "simple therapy" and had unacceptable HbA_{1c} levels; while taking maximal doses of at least one oral antidiabetes drug, insulin, or both. Their average level was 9.5%, whereas normal is 6%. This population, he added, was at higher risk than those in other outcome studies, with 40.4% having had prior CVD events, 80% having hypertension, more than 50% having lipid abnormalities, and the majority being obese.

Presenting preliminary findings, Dr. Abraira pointed out that although a direct relationship between glucose levels and CVD has been shown, prior studies have failed to demonstrate a significant CVD event risk reduction from good glycemic control.

The VADT trial enrolled 1,791 U.S. veterans from 20 centers. All participants were treated intensively with drugs and lifestyle therapies to control blood pressure and blood lipid levels. Half the participants were randomly assigned to the intensive blood glucose control group, and the other half were assigned to the standard control group. Patients were followed for an average of 6.25 years.

All patients received oral drugs and insulin as needed; 90% of the intensive-therapy group and 74% of the standard group eventually used insulin, and slightly more individuals in the intensive group took oral drugs. Within six months, the intensive group achieved a median HbA_{1c} of 6.9%, the standard group, 8.4%. The average difference for the duration of the trial was 1.5% between the groups. The primary endpoint of composite CVD events was reported in 29.3% of patients in the standard-treatment glucose control group and in 25.9% of the intensive-treatment control group ($P = 0.11$).

"There was no significant effect of glucose control on cardiovascular events," Dr. Duckworth said.

Differences in time to primary outcome were also not significant ($P = 0.12$). Among predictors of first primary outcome were prior events, age, duration of diabetes, lower high-density lipoprotein-cholesterol (HDL-C) levels, higher HbA_{1c} values, and hypoglycemia. Among predictors of cardiovascular death (hypoglycemia, HbA_{1c}, HDL-C, age, prior events), the strongest was recent severe hypoglycemia, with a hazard ratio of 4.042.

Although hypoglycemia was a stronger predictor of death in the standard-treatment glucose-lowering group than in the intensive-treatment group, severe hypoglycemia (defined as causing either impaired or total loss of consciousness) was more frequent with intensive treatment (21.1% vs. 9.7%). Severe hypoglycemia was also a significant predictor of CVD events ($P = 0.002$).

An analysis of the interaction between intensive therapy and diabetes duration showed that intensive therapy was initially protective, especially if it was initiated soon after diagnosis of diabetes. However, as the duration of diabetes increased (15 years), the benefit disappeared.

"Intensive glucose control may be detrimental in long-established type-2 diabetes," Dr. Duckworth said.

In an ADA press conference, Dr. Abraira commented, "I'm not ready to make any recommendations. Diabetes is extremely complicated, and I'm not sure I know anything for certain. This is a work in progress."

Dr. Duckworth said, "I think stating target goals of HbA_{1c} for everybody is wrong. I treat patients, not numbers."

Sitagliptin (Januvia) plus Metformin (Glucophage)

- Deborah Williams-Herman, MD, Merck Research Laboratories, Rahway, N.J.
- Priscilla Hollander, MD, Baylor University Medical Center, Dallas, Tex.

In a study of initial therapy for type-2 diabetes mellitus with sitagliptin (Januvia, Merck) and metformin (Glucophage), the combination led to sustained improvements in both beta-cell function and in HbA_{1c} values. Dr. Williams-Herman presented the results of the study, which included a 104-week extension among 587 patients. In the study's first 24 weeks, 1,091 patients received the sitagliptin/metformin combination or placebo. An active-treatment phase followed in which the 762 placebo subjects were switched to metformin. Evaluable patients in the extension phase (n = 402) received one of five treatment regimens:

- sitagliptin 50 mg twice daily plus metformin 500 mg twice daily (n = 96)
- sitagliptin 50 mg twice daily plus metformin 1,000 mg twice daily (n = 105)
- metformin 1,000 mg twice daily (n = 87)
- metformin 500 mg twice daily (n = 67)
- sitagliptin 100 mg daily (n = 50)

Beta-cell function was analyzed in 125 self-selected subjects who underwent a frequently sampled standard meal-tolerance test at baseline and again at week 104.

Dr. Williams-Herman reported substantial improvements in the steady-state rate of insulin secretion as a function of glucose concentration (median increases from baseline: group 1, 20.2; group 2, 22.5; group 3, 10.4; group 4, 9.8; and group 5, 13.6). Mean HbA_{1c} levels also decreased from baseline: group 1, 1.4%; group 2, 1.7%; group 3, 1.3%; group 4, 1.1%; and group 5, 1.2%.

The data for the sitagliptin/metformin combination, Dr. Williams-Herman said, "translate to an increased responsivity of the beta cell to glucose and to HbA_{1c} lowering."

Dr. Hollander reinforced that viewpoint in an interview:

> Type-2 diabetes is defined now as a disease of beta-cell deterioration over time requiring increasing levels of treatment to maintain the type of glucose control we would like. Although we have not previously thought of metformin as a drug that increases beta-cell function, these data show that sitagliptin and metformin make an attractive combination that may offer some longer durability of treatment without having to increase therapy. ■