MEETING HIGHLIGHTS

American Diabetes Association
and
European League Against Rheumatism

Walter Alexander

More than 12,000 health care professionals attended the 69th Annual Scientific Sessions of the American Diabetes Association from June 5 to 9, 2009, in New Orleans, Louisiana. Included in this article are key sessions concerning the long-term efficacy and cardiovascular risks in the pharmacological treatment of type-2 diabetes.

Sitagliptin with or without Metformin In Type-2 Diabetes

Debora Williams-Herman, MD, Senior Researcher, Merck Research Laboratories, Rahway, N.J.

A two-year study of sitagliptin (Januvia, Merck) with or without metformin demonstrated that treatment enabled patients with type-2 diabetes to achieve substantial and safe improvements in glycemic control.

“This is the first report on long-term, 104-week data for type-2 diabetes patients treated with sitagliptin, either as monotherapy or as add-on therapy to metformin (e.g., Glucophage, Bristol-Myers Squibb). And both cohorts achieved mean glycosylated hemoglobin (HbA₁c) levels of 6.9% at two years,” said Dr. Williams-Herman, presenter and lead author.

For their analysis of sitagliptin monotherapy, investigators pooled data from two clinical trials. They evaluated HbA₁c responses among 147 subjects with common baseline characteristics (HbA₁c, 7.5%–10%) who were not taking an antihyperglycemic drug at screening.

To analyze the efficacy of sitagliptin added to metformin, investigators pooled data from two other clinical trials that included 852 subjects with common baseline characteristics (HbA₁c, 7%–10%) who were receiving metformin 1,500 mg/day or more at screening. Data gathered after glycemic rescue were excluded.

In the patients receiving sitagliptin monotherapy, their mean baseline age was 53 years, mean baseline HbA₁c was 8.5%, mean baseline fasting plasma glucose level was 187 mg/dL, and mean baseline time since the diagnosis of type-2 diabetes was 4.9 years. At 104 weeks, these patients achieved a mean decrease in HbA₁c from 8.5% at baseline to 6.9%.

In the patients receiving sitagliptin plus ongoing metformin, their mean baseline age was 56 years, mean baseline HbA₁c was 8%, mean baseline fasting plasma glucose level was 173 mg/dL, and mean baseline time since the diagnosis of type-2 diabetes was 6.5 years. At 104 weeks, these patients achieved a mean decrease in HbA₁c from 8% at baseline to 6.9%.

Sitagliptin was generally well tolerated over two years in each of the four clinical trials included in the study. The authors concluded:

“In summary, sitagliptin as monotherapy, or as add-on therapy to metformin in patients with type-2 diabetes, provided substantial improvement in glycemic control over two years.”

RECORD: Five-Year Results for Rosiglitazone And Cardiovascular Risk

Philip Home, DM, DPhil, Professor of Diabetes Medicine, Newcastle University, Newcastle, U.K.

In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone (Avandia, GlaxoSmithKline) plus standard therapy did not increase the risk of cardiovascular disease or death in the treatment of type-2 diabetes, but some safety concerns remain.

Reporting RECORD results, Dr. Home, lead investigator, said:

“We confirmed the overall cardiovascular safety of rosiglitazone in over 4,000 subjects. And for a composite of cardiovascular death, stroke, and heart attack, we found that rosiglitazone was slightly better that metformin and sulfonylureas.”

The RECORD investigators also found that rosiglitazone increased the specific risk of heart failure as well as the risk of fractures. They randomly assigned 4,447 patients with a mean HbA₁c of 7.9% who were already being treated with metformin or a sulfonylurea. Patients in the active-treatment group received add-on rosiglitazone (n=2,220). Controls (n=2,227) already receiving metformin were given a sulfonylurea in addition, and those control patients already receiving a sulfonylurea were also given metformin. The primary endpoint of the study was hospitalization or death resulting from a cardiovascular event.

Dr. Home reported cardiovascular hospitalization or cardiovascular death in 321 rosiglitazone patients compared with 323 controls. The difference was not statistically significant for the primary endpoint.

Heart failure that resulted in a hospital admission or death was reported in 61 rosiglitazone patients and in 29 controls, representing more than a doubling of risk for rosiglitazone. The risk of fracture of the arm and lower leg also increased among rosiglitazone patients at a rate of 82% for women and 23% for men. Regarding the clinical implications, Dr. Home concluded:

The author is a freelance medical writer living in New York City.
Rosiglitazone is not recommended for people with a history of heart failure or with previous problems that might have led to myocardial dysfunction. Rosiglitazone should be used with caution in women at high risk of fractures. Although our evidence is insufficient to rule out a small increased risk of myocardial infarction caused by rosiglitazone when compared with other glucose-lowering agents, rosiglitazone does not increase overall cardiovascular morbidity or mortality.

**ACCORD and VADT Update: Glucose Lowering and Cardiovascular Risk**

- Matthew C. Riddle, MD, Oregon Health & Sciences University, Portland, Ore.
- William C. Duckworth, MD, University of Arizona, Phoenix, Ariz.

Ongoing analyses of data from two major trials suggest that intensive lowering of HbA1c levels reduces cardiovascular risk in patients with type-2 diabetes and does not generally increase the risk of cardiovascular events for these patients.

In a press briefing held in the closing hours of the ADA meeting, researchers reported new findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Veterans Affairs Diabetes Trial (VADT). Last year, researchers conducting these trials reported that intensifying antiglycemic treatment in an effort to achieve HbA1c levels below 7% did not reduce the risk of cardiovascular events; in ACCORD, however, such risks actually increased.

After more analyses of subpopulations, researchers from both trials have reported that subjects who achieved HbA1c below 7% had lower cardiovascular risks than those who did not achieve this HbA1c goal.

Dr. Riddle, ACCORD lead author and investigator, said: “An HbA1c [level] below 7% alone does not appear to explain the excess deaths in the ACCORD trial and is not necessarily a predictor of mortality risk. Further, the rate of one-year change in HbA1c showed that a greater decline in HbA1c was associated with a lower risk of death.”

Discussing the discrepancy from last year’s report at the ADA conference, he added: “It appears that people who did not attain HbA1c goals might have had behavioral problems affecting adherence to treatment or diet or physiological differences from other participants, including other diseases.”

Applying new perspective to VADT findings, lead author Dr. Duckworth explained that upon further data analysis, starting intensive glucose control in the first 15 years after a diagnosis of type-2 diabetes reduced the risk of cardiovascular events, including mortality; however, starting glycemic control 16 to 20 years after the diagnosis showed no such benefit. Analyses of data from both ACCORD and VADT are ongoing.

**European League Against Rheumatism**

**The GO-AFTER Trial and TNF Blockers**

- Josef Smolen, MD, Professor of Medicine, Medical University of Vienna, Vienna, Austria

Patients with rheumatoid arthritis (RA) who had already been treated with adalimumab (Humira, Abbott), etanercept (Enbrel, Amgen/Wyeth) or infliximab (Remicade, Centocor Ortho Biotech Inc.) responded well to golimumab (Simponi, Centocor Ortho Biotech Inc.). This was the result, no matter which anti–tumor necrosis factor (TNF) therapy they had received or why they discontinued, reported researchers from the GO-AFTER (GOlimumab After Former anti-TNF Therapy Evaluated in Rheumatoid Arthritis) trial. Dr. Smolen, presenter and lead investigator, explained:

To this point, we have been using, and without sufficient data, alternative TNF-inhibitors after other TNF-inhibitors failed. This is the very first randomized, double-blind, controlled clinical trial looking at a new TNF-inhibitor, golimumab, in patients who failed to respond to one, two, or three other TNF-inhibitors. We see efficacy for golimumab used in this way, and inhibition of TNF with golimumab can occur when other TNF-inhibitors have failed for a variety of reasons.

Patients enrolled in GO-AFTER had received one or more anti-TNF agents, which they subsequently discontinued. They had also been allowed concomitant treatment with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, and hydroxychloroquine. The patients were randomly assigned to one of three treatment groups: subcutaneous (SQ) placebo, golimumab 50 mg or golimumab 100 mg every four weeks.

The researchers performed subgroup analyses to determine American College of Radiology responses of ACR20 at week 14 for DMARD use, the number of prior anti-TNF blockers, and discontinuation of prior TNF-inhibitor therapy for any reason. (To achieve an ACR20 response, a patient must have a 20% reduction in the number of swollen and tender joints and a reduction of 20% in three of these parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and degree of disability in the Health Assessment Questionnaire score.)

The authors then calculated the overall response to golimumab by comparing the proportions of ACR20 responders at week 14 in the combined golimumab groups with the placebo groups. Data for the cohort who had received only one
prior anti-TNF therapy were also analyzed to evaluate the effect of TNF-inhibitor type on golimumab response. Adverse events were evaluated for the various subgroups.

Comparing proportions of ACR20 responders at week 14, the researchers reported that golimumab was more effective than placebo in patients who had previously used one or more anti-TNF agents, irrespective of why prior anti-TNF treatment was discontinued.

In patients who had previously stopped therapy because of a lack of efficacy, the ACR20 rate with golimumab was higher (39%, in 68 of 173 patients) when compared with placebo (18%, in 17 of 96 patients) \( (P < 0.001) \). For those discontinuing prior anti-TNF therapy for other reasons, golimumab outperformed placebo with an ACR20 rate of 34% in 55 of 162 patients versus a rate of 20% in 17 of 84 patients \( (P = 0.027) \).

The ACR20 rate was higher in the golimumab group than in patients who received concomitant DMARDs. Rates were as follows:

- DMARDs plus golimumab (40%, 86 of 215 patients) versus DMARDs plus placebo (18%, 19 of 107 patients) \( (P < 0.001) \)
- no DMARDs: golimumab (29%, 26 of 89 patients) versus placebo (19, 9 of 48 patients) \( (P = 0.184, \text{not significant}) \)

The investigators also found significantly greater ACR20 efficacy for golimumab than for placebo for prior use of one anti-TNF blocker (39% in 82 of 213 patients) versus 20% in 18 of 90 patients, respectively \( (P = 0.002) \) and with the prior use of two anti-TNF-inhibitors (38% in 27 of 71 patients) versus 16% \( (7 \text{ of } 44 \text{ patients}) (P = 0.014) \).

Of the previously treated patients, 80% had received prior anti-TNF therapy for 12 weeks or more, and 49% had received such therapy for 48 weeks or more. Golimumab was effective regardless of the anti-TNF type received previously.

Adverse events through week 24 were similar for both the placebo and golimumab groups; for patients who had previously received only adalimumab, etanercept, or infliximab; and for those who had received one, two, or three previous anti-TNF agents.

The authors concluded:

“These data suggest that patients previously treated with adalimumab, etanercept, or infliximab responded to and tolerated golimumab, regardless of the type, number, or reason for discontinuation of prior anti-TNF therapy.”

Too few patients received three previous anti-TNF agents to provide conclusive results for that group.

**AIM Extension Study: Abatacept (Orencia) and Rheumatoid Arthritis After Five Years**

- Harry Genant, MD, Professor Emeritus of Radiology, Orthopedic Surgery, Medicine, and Epidemiology, and Executive Director, Osteoporosis and Arthritis Research Group, Department of Radiology, University of California—San Francisco

Patients with RA who responded inadequately to methotrexate and who were treated with abatacept (Orencia, Bristol-Myers Squibb) were able to experience inhibition of structural damage for up to five years.

Dr. Genant, lead investigator of a long-term extension of a one-year phase 3, randomized, double-blind, placebo-controlled trial, stated:

“No doubt, we found that with time, there is increasing effectiveness with abatacept treatment rather than loss of effectiveness. The percentage of patients and the magnitude of the destructive change dropped sequentially every year over the five years of the study.”

In the earlier study (AIM, or Abatacept in Inadequate Responders to Methotrexate), patients had received approximately 10 mg/kg of abatacept (according to weight) or placebo plus methotrexate on days 1, 15, and 29 and then every four weeks. Patients who completed the double-blind phase were eligible to participate in the extension study. Radiographs of hands and feet were taken at the baseline evaluation and at years 1 through 5 or on early termination. All radiographs were re-read at year 5 and were scored for disease progression. Investigators scored paired radiographs for erosion, joint-space narrowing, and total score using the Genant-modified Sharp score. Patients with total scores below or equal to zero were classified as “non-progressors” (i.e., showing no progression of structural damage).

Among patients who had initially received abatacept and who participated in the extension study \( (n = 378) \), 291 patients \( (77\%) \) had paired radiographs both at baseline and at year 1; 290 \( (77\%) \), at baseline and at year 2; 293 \( (78\%) \), at baseline and at year 3; 287 \( (76\%) \), at baseline and at year 4; and 235 \( (62\%) \), at baseline and at year 5, respectively. There was a reduction of approximately 50% in erosion, joint-space narrowing, and total scores in the second year as compared with the first year. Decreases in all three measures continued over the third, fourth, and fifth years.

During the five years, the following patients were considered to be non-progressors:

- at the first year, 173 patients \( (59,575) \)
- at the second year, 143 patients \( (49,3\%) \)
- at the third year, 134 patients \( (45,7\%) \)
- at the fourth year, 128 patients \( (44,6\%) \)
- at the fifth year, 106 patients \( (45,1\%) \)

Among the non-progressors,

- at the first year, 76% remained non-progressors at year 2.
- at the first and second years, 88% remained non-progressors at year 3.
- during years first to third years, 92% remained non-progressors at year 4.
- during the first to fourth years, 98% remained non-progressors at year 5.

“The percentage of patients and the magnitude of the destructive change dropped sequentially every year over the five years of the study,” added Dr. Genant.