Candesartan Has DIRECT Effects on Retinopathy

BY SARA FREEMAN
Contributing Writer

ROME — Candesartan helped prevent the development of new retinopathy in patients with type 1 diabetes, and prevented worsening eye disease in patients with type 1 and type 2 diabetes, data from an international study program showed. This was true even though the primary end points of the individual studies were not met.

Evidence also suggested that the angiotensin II receptor blocker (ARB) increased the probability of regression of existing eye disease by 34% in patients with type 2 diabetes.

These findings come from the Diabetic Retinopathy Candesartan Trials (DIRECT) program presented at the annual meeting of the European Association for the Study of Diabetes; they are also being published in the Lancet. The findings are the first to show that ARBs could have a direct effect on diabetic retinopathy in normoalbuminuric and normotensive type 1 diabetes patients, or in mildly hypertensive (but treated) type 2 individuals. These data also add to accumulating evidence that these drugs do more than just lower blood pressure.

The finding that candesartan may increase the likelihood of regression in type 2 diabetes is particularly important, since "diabetic eye disease in type 2 patients is very difficult to treat with good effect," said Dr. Anne Katrin Sjølie, professor of ophthalmology at Odense University Hospital, Denmark. She spoke during a press briefing on the DIRECT program ahead of the formal presentation of the results.

Dr. Sjølie, chair of the DIRECT steering committee that is funded by AstraZeneca and Takeda, noted that the trials program consisted of three randomized controlled studies involving 5,231 patients: DIRECT-PREVENT 1, DIRECT-PROTECT 1, and DIRECT-PROTECT 2. The development or worsening of retinopathy was measured in all these trials as a two- or three-step change on the 11-point Early Treatment of Diabetic Retinopathy Study (ETDRS) scale. This scale uses photographs of the retina to gauge the level and severity of diabetic eye disease.

In DIRECT-PREVENT 1, 711 patients with type 1 diabetes and no existing eye disease were randomized to treatment with candesartan, and another 710 were randomized to placebo. Candesartan reduced the primary end point of the incidence of retinopathy (two-step ETDRS change) by 18% compared with placebo, which was not statistically significant.

However, Dr. Nishi Chaturvedi, professor of clinical epidemiology at Imperial College London, who presented the findings of the DIRECT-PREVENT 1 trial, commented that a significant 35% difference was observed when a three-step change in the ETDRS scale was used in a posttrial analysis. This was largely unaffected by adjustment for baseline diabetes duration and hemoglobin A_{1c}. "The reason we did this is in order to compare our findings with previous studies to put them into context," she explained.

Dr. Chaturvedi also showed data from the DIRECT-PROTECT 1 trial, which used a three-step change in the ETDRS scale as its primary end point to see if candesartan could prevent the progression of worsening retinopathy in patients with type 1 diabetes. In this trial there were 951 candesartan- and 954 placebo-treated patients, but no significant difference was seen between the groups in terms of retinopathy progression.

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DR. HANSSEN

The primary end point of the DIRECT-PROTECT 2 trial also was not met, said Dr. Sjølie, and this was the prevention of worsening retinopathy—again measured by a three-step change in the ETDRS—in patients with type 2 diabetes with existing eye disease, of whom there were 951 treated with the ARB and 954 with placebo. A nonsignificant 13% reduction in retinopathy progression was observed, which did not change greatly when a prespecified adjustment for baseline level of retinopathy, diabetes duration, HbA_{1c}, urinary albumin excretion rate, systolic blood pressure, or antihypertensive therapy was made. Dr. Sjølie noted, however, there was a 34% improvement in retinopathy regression—a prespecified secondary end point of this study.

In all three studies there were no undue safety concerns, and 80% of the patients given candesartan received a daily dose of 32 mg for 4-6 years, the study sponsors noted in a press release.

Pooled data from the three trials on the effects of candesartan versus placebo on the development of new microalbuminuria were presented by Dr. Rudy Bilous, professor of clinical medicine at the University of Newcastle, England. The data showed no significant benefit of active treatment on this parameter.

The cumulative incidence of microalbuminuria in the trial was small, however, which perhaps reflected the young age of the patients participating in the program. The mean age of patients was approximately 29 years in DIRECT-PREVENT 1, 31 years in DIRECT-PROTECT 1, and 56 years in DIRECT-PREVENT 2.

"We conclude that treatment with candesartan may confer benefit for retinopathy in people with diabetes," Dr. Bilous said.

"We will never again have such a large study in diabetic retinopathy," observed Dr. Kristian Hanssen, an independent commentator and professor of medicine at Aker University Hospital in Oslo. He suggested that it probably doesn't matter whether patients use an ARB or an ACE inhibitor; maintaining a low blood pressure—possibly as low as 120/80 mm Hg—is what's important.

"The take-home message is ARBs or ACE inhibitors are indicated in patients with risk of progression into retinopathy," Dr. Hanssen said. They should also be considered in those patients with existing eye disease. The study data, together with those from other large-scale studies, should be used to create a "risk engine" to help clinicians diagnose retinopathy in their patients.

Dr. Sjolie, Dr. Chaturvedi, and Dr. Bilous disclosed receiving honoraria to attend DIRECT steering committee meetings from the study program's sponsors, AstraZeneca and Takeda. Dr. Hanssen reported no conflicts of interest. ■

Culturally Based Diabetes Education Aids Glycemic Control

BY HEIDI SPLETE
Senior Writer

Culturally based type 2 diabetes education programs improved patients' glycemic control for at least 6 months, based on results from a meta-analysis of 11 studies involving more than 1,000 patients.

"In some cases, cultural and communication barriers increase the problems minority ethnic communities experience in accessing good quality diabetes health education, a vital aspect contributing towards patient understanding, use of services, empowerment, and behaviour change towards healthier lifestyles," the reviewers wrote in a report by the Cochrane Collaboration published online.

Overall, findings from the studies showed significant improvement in glycemic control (as measured by hemoglobin A_{1c} levels) at 3- and 6-month follow-ups among patients who received culturally appropriate health education interventions, compared with control patients who received standard health education (described as "usual care"). This finding is clinically important if the improvement can be sustained, the reviewers noted, but the improvement in glycemic control was not significantly different between the groups at 12 months after the intervention.

In addition, patients in the intervention group showed significantly improved knowledge about diabetes and healthy lifestyles, compared with the control group at 3, 6, and 12 months after the intervention.

The report consisted of data from 11 trials including 1,603 individuals at least 16 years old who had type 2 diabetes. The patients were members of ethnic-minority groups in upper-middle–income or high-income countries. Previous studies have suggested that ethnic minorities in these countries have higher rates of type 2 diabetes, compared with the majority populations, and the investigators who conducted the studies theorized that culturally appropriate education would improve diabetes management in ethnic-minority patients. The primary outcome measure was glycemic control.

The studies included in the review took place in Europe, the United States, Canada, South Africa, New Zealand, and Australia. In most of the studies, the intervention was repeated several times for periods lasting from 6 to 12 weeks. None of the studies followed patients for more than 12 months from the start of the intervention (Cochrane Database Syst. Rev. 2008 [doi: 10.1002/14651858.CD006424.pub2]).

Culturally appropriate health education intervention was defined as "education that is tailored to the cultural or religious beliefs and linguistic skills of the community being approached, taking into account likely literacy skills," the researchers wrote. The intervention strategies varied among the studies and included using community-based health advocates, providing education to same-gender groups, and adapting dietary advice to fit a community's available food options.

No significant improvements were found in most of the other clinical outcomes measured in the studies (including triglycerides, blood pressure, or weight) between patients who received culturally appropriate education intervention and those who received usual care. Total cholesterol was the exception—the intervention patients showed improvement in total cholesterol at 12 months, but not at 3 months or 6 months, compared with the control patients, based on data from the three studies that addressed this outcome.

No significant differences in quality of life were reported between patients who received culturally appropriate diabetes education and those who received standard education, according to findings from the three studies that addressed quality of life.

Despite the short duration of improvement, the findings suggest that culturally appropriate education programs can make a significant difference in diabetes control and are worth developing, the reviewers said.

"It has been known for some time that diabetes health education improves knowledge about diabetes as well as blood glucose control, but this review has shown that culturally appropriate health education is better than 'normal' practice for minority communities," they wrote. "The results strengthen the belief, based on educational theory, that health education should be couched in a learner-centered manner that respects their religious, social, and cultural values in order to have the most impact."

The lead review author, Dr. Kamila Hawthorne of Cardiff (Wales) University, was the author of one of the studies included in the review. The other reviewers had no conflicts of interest to disclose. ■