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 findings 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 post-hoc analysis. This was largely unaffected by adjustment for baseline diabetes duration and hemoglobin A1c. “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.

The primary end point of the DIRECT-PROTECT 2 trial was similar to that in DIRECT-PREVENT 1, 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 the incidence of retinopathy progression was observed, which did not change greatly when a prespecified adjustment for baseline level of retinopathy, diabetes duration, HbA1c, 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.

Pooleed 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-PROTECT 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 Hansson, 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, compared with a placebo, as long as blood pressure is controlled—is the young age of the patients the key?

“The take-home message is ARBs or ACE inhibitors are indicated in patients with risk of progression into retinopathy,” Dr. Hansson 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. Sjølie, Dr. Chaturvedi, and Dr. Bilous disclosed receiving honoraria to attend DIRECT steering committee meetings from the study program’s sponsors, AstraZeneca and Takeda. Dr. Hansson 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,” the researchers wrote. The intervention strategies addressed this outcome.

Culturally appropriate diabetes education 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 ‘usual’ care and is worth developing,” the reviewers said.

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