

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

Abstract:

Diabetic retinopathy is a micro vascular complication of diabetes mellitus. It is a retinal vascular disorder and is characterised by signs of retinal ischemia and/or signs of increased retinal vascular permeability. Diabetic retinopathy is a progressive condition by nature and is a leading cause of blindness worldwide. With this information in mind, the recent article in the New England Journal of Medicine entitled "Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes" makes for interesting reading. This publication describes a subgroup study of the larger ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial.

The beneficial effects of tight glycaemic and blood pressure control on the progression of diabetic retinopathy in persons with type 2 diabetes have been shown. ACCORD was designed to assess the effects of specific strategies for managing blood glucose levels, blood pressure and in addition serum lipid levels in 10,251 participants with type 2 diabetes mellitus who had either established cardiovascular disease or known cardiovascular risk factors. It was a randomised trial conducted at 17 clinical sites in the United States and Canada. ACCORD was sponsored by the National Heart Lung and Blood institute and study drugs were donated by the manufacturers.

The ACCORD eye study included 2,856 participants. Of note, patients, who, at baseline had a history of proliferative diabetic retinopathy that had been treated with laser photocoagulation or vitrectomy were excluded. Participants had eye exams and retinal photography at baseline and year 4 and were graded according to a 17-step scale. Visual acuity was measured every 2 years. The primary aim was to determine whether any of the three interventions evaluated in the ACCORD trial reduced the risk of development or progression of diabetic retinopathy. The first significant finding of the ACCORD eye study was that intensive glycaemic control (target HbA1c <6%) versus standard glycaemic control (target HbA1c 7.0 - 7.9%) resulted in a 33% reduction in the risk of progression of diabetic retinopathy over a relatively short period of 4 years. This management strategy was however associated with a higher risk of having a significant hypoglycaemic event and an increased rate of death from any cause after a mean of 3.5 years of follow up.

The most dramatic finding was the beneficial effect of fenofibrate therapy in combination with a statin. With only a very modest difference in mean serum triglycerides of 0.3 mmol/L between the group taking simvastatin and fenofibrate when compared to the group taking simvastatin alone, there was a 40% reduction in the odds of having a progression of diabetic retinopathy over the 4 years. These results were adjusted to exclude the effects of glycaemia. These findings are in keeping with The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study which was a randomised trial of mono therapy with fenofibrate and showed a significant reduction in the need for laser therapy for either macular oedema or proliferative retinopathy in the fenofibrate group as compared with the placebo group. However, this was not associated with a concomitant reduction in serum triglyceride levels, suggesting that the enhanced effect of fenofibrate in the ACCORD Eye study may be the result of an interaction with simvastatin.

The final arm of the study looked at the effect of intensive versus standard blood pressure control on diabetic retinopathy. A benefit of intensive blood pressure control was not demonstrated. This is in contrast to the United Kingdom Prospective Diabetes Study (UKPDS) which did demonstrate a significant reduction in the progression of diabetic retinopathy and a significant reduction in moderate vision loss after 7.5 years. However, the blood pressures in UKPDS were a higher range and the duration of treatment was longer. There was no significant beneficial effect on moderate vision loss in any of the three arms of the trial as measured by deterioration of visual acuity. The report of the ACCORD eye study provides information regarding diabetic retinopathy and strategies that may be employed to limit its progression. The study reassures us that aiming for optimal glycaemic control will assist in preventing this adverse outcome. ACCORD however, does highlight that there are risks and benefits to all management plans and one should consider this when tailoring individual patient goals. In addition, it is still not entirely clear why exactly tight glycaemic control was associated with an increased risk of death in the original trial. Although the ACCORD eye study does not demonstrate a beneficial effect of tight blood pressure control on retinopathy progression, we continue to advocate treating to the target blood pressure of <130/80mmHg.

This study draws attention to the importance of lipid management in

persons with type 2 diabetes. The target triglyceride level suggested by the American Diabetes Association is 1.7 mmol/L⁶. Unfortunately in clinical practice this goal is often not reached. The findings of this study suggest the need for further evaluation to establish the potential role of fenofibrates in the treatment of diabetic retinopathy. Further research will likely look closer at fibrates to assess if they do have an effect on retinopathy progression independent of the reduction in serum triglycerides.

A Egan, M Byrne
Department of Endocrinology & Diabetes Mellitus, Mater Misericordiae
University Hospital, Eccles St, Dublin 7

References

1. Kempen JH, Oâ Colmain BJ, Leske MC, Haffner SM, Klein R, Moss SE, Taylor HR, Hammann RF. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol.* 2004; 122:552-563.
2. The ACCORD Study Group and ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010; 363:233-244.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
4. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. *N Engl J Med* 2008; 358:2545-2559.
5. Keech AC, Mitchell P, Summanen PA, Oâ Day j, Davis TM, Moffitt MS, Taskinen MR, Simes RJ, Tse D, Williamson E, Merrifield A, Laatikainen LT, dâ Emden MC, Crimet DC, Oâ Connell RL, Colman PG; Field Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007;370:1687-97.
6. American diabetes association position statement. Standards of medical care in diabetes. *Diabetes Care* 2010;33: S1.

Comments: