ABSTRACT

A number of clinical trials have shown that it is possible to significantly modify the course of diabetic retinopathy (DR) and diabetic macular edema (DME) using laser therapy. Pharmacologic treatments to slow the progression of DR have produced inconsistent results. Although intensive diabetes treatment strategies designed to produce tight control of glucose, lipids, and blood pressure have significantly improved DR, aldose reductase inhibitors and aspirin have not been clearly beneficial. Inhibition of protein kinase C activity with ruboxistaurin did not significantly affect the progression of DR but did reduce the progression of central DME and moderate vision loss. Other new treatment approaches are currently being evaluated for DR, including injection of intravitreal steroids, inhibitors of vascular endothelial growth factor and growth hormone, and the combination of photocoagulation and pharmacologic treatment. The National Eye Institute has recently begun to develop a nationwide network of clinical research centers to evaluate new treatments for DR.


PHARMACOTHERAPY FOR DR

As described by Dr Lloyd P. Aiello elsewhere in this monograph, it is now possible to dramatically improve the course of proliferative diabetic retinopathy (PDR) using laser treatment. Laser therapy has been shown to prevent vision loss and to slow the progression to PDR, although it is not effective for all patients, and additional treatment approaches are required to further reduce the progression of diabetic retinopathy (DR). Current laser therapies for diabetic macular edema (DME) are somewhat less effective. Pharmacotherapy strategies to prevent DR progression have been evaluated in a number of controlled clinical trials including the Sorbinil Retinopathy Trial, the Early Treatment Diabetic Retinopathy Study (ETDRS), the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), and the recent Protein Kinase C-Diabetic Retinopathy and PKC-Diabetic Macular Edema trials. These studies have demonstrated that pharmacologic treatments significantly slow the progression of retinal injury and vision loss in some patients with diabetes.
median duration of 41 months. Sorbinil administration did not significantly improve the course of retinopathy, as assessed by several outcome measures including the proportion of patients with 2-level worsening on a modified ETDRS rating scale, mean change in retinopathy severity score from baseline, or the number of retinal microaneurysms (Figure 1). There are newer aldose reductase inhibitors that are more potent than sorbinil, but the cost of a large retinopathy trial and the history of negative outcomes with aldose reductase inhibitors has made it very difficult for researchers to conduct well-controlled clinical trials of these newer agents.

Although the ETDRS is usually described as a photocoagulation trial, it also included an evaluation of antiplatelet therapy using aspirin. There had been some conjecture before the trial that antiplatelet therapy might slow the progression of DR. The ETDRS evaluated the combination of photocoagulation and aspirin for the treatment of mild to severe nonproliferative DR (NPDR) or early PDR. A total of 3711 patients were randomly assigned to receive aspirin (650 mg/day) or placebo. In addition, one eye of each patient was randomly assigned to deferral of photocoagulation and the other eye to early photocoagulation. Aspirin therapy had no effect on the progression of retinopathy, the development of high-risk PDR, or the risk of visual loss. A subsequent analysis from this study found that aspirin also had no effect on the rate or the severity of vitreous or preretinal hemorrhage.

In contrast, the DCCT conclusively showed that over a period of several years, intensive blood glucose management was associated with a marked reduction in the number of patients with DR at enrollment who exhibited a worsening of at least 3 steps on the ETDRS rating scale. A total of 1441 patients with type 1 diabetes were randomized to intensive diabetes therapy or conventional treatment for up to 10 years. The patients were subdivided into a primary prevention cohort (patients with no retinopathy at baseline; n = 726) and a secondary prevention cohort (patients with mild retinopathy at baseline; n = 715). Intensive therapy with either 3 or more daily insulin injections or an insulin pump was associated with a 54% reduction in the rate of progression of DR among the cohort of patients with mild DR at enrollment.

Other pharmacologic treatment strategies have also been shown to reduce the risk of microvascular complications of diabetes, including the progression of DR. The relationship between blood pressure (BP) and DR was evaluated in a substudy of the UKPDS, in which 1148 patients with type 2 diabetes and hypertension were randomized to either tight BP control (target BP of <150/85 mm Hg) or less-tight BP control (target BP of <180/105 mm Hg). After a median follow-up of 8.4 years, patients in the tight BP control group exhibited a 37% relative reduction in the risk of any microvascular outcome (P = .0092). This reduction in microvascular disease was primarily the result of a decrease in the need for retinal photocoagulation. By the end of the study, tight BP control was associated with a 47% relative reduction in the risk of a decrease of 3 or more steps on the ETDRS rating scale from baseline (10.2% vs 19.4% of patients for the tight and less-tight BP control groups, respectively; P = .0036). In addition, some data have shown that serum cholesterol is associated with the formation of hard exudates and progressive vision loss. The effects of serum lipid concentrations on DR progression were examined in the ETDRS study, which enrolled patients who had mild NPDR with DME, or moderate NPDR through mild PDR either with or without DME. Macular hard exudates at baseline were categorized as rare, questionable, definite, obvious, moderate, and severe. As shown in Figure 2, the rating of retinal hard exudates was significantly associated with
increasing total cholesterol concentration ($P < .001$). Hard exudates were also significantly associated with increasing low-density lipoprotein cholesterol concentration ($P < .001$). A decrease in visual acuity (defined as a doubling of the visual angle) over 5 years was also significantly associated with hard exudate severity (Figure 3; $P = .002$). The incidence of visual loss was 50% greater among patients with elevated cholesterol (>240 mg/dL) than among patients with cholesterol values under 200 mg/dL.

**Diabetic Macular Edema**

Established pharmacologic approaches to prevent the progression of DME include control of blood glucose, BP, and serum lipids.$^{14-16}$ Several new treatments are also being developed for DME, including inhibition of vascular endothelial growth factor (VEGF), anti-inflammatory agents, and inhibition of protein kinase C (PKC). VEGF stimulates the development of new retinal blood vessels in response to retinal ischemia and increases vascular permeability, contributing to the formation of edema and hard exudate deposits.$^{17}$ Animal models have suggested that the inhibition of VEGF activity can prevent the development of retinal neovascularization,$^{18}$ and VEGF inhibitors are currently being evaluated in clinical trials for the prevention of DME.$^{17}$ Intravitreal steroids have also received increasing attention for the treatment of DME. Steroids are believed to inhibit prostaglandin production and also to prevent increased vascular permeability at vascular tight junctions, which is thought to occur as a result of VEGF activity.$^{19,20}$ Many clinicians were impressed by fundus photographs and optical coherence tomography (OCT) findings demonstrating the effectiveness of intravitreal steroid injection.$^{21}$ Although there are few randomized clinical studies, some noncomparative case series studies have suggested that intravitreal steroid injection also improves visual function.$^{19,21}$ Intravitreal steroid injection is associated with potentially serious side effects such as bacterial infection of the eye, vitreous hemorrhage, cataracts, glaucoma, and sterile inflammatory reactions that may be caused by a component of the excipient.$^{20}$

The effects of PKC inhibition with ruboxistaurin in DME were examined in the recent Protein Kinase C-Diabetic Macular Edema Study (PKC-DMES) clinical trial.$^7$ A total of 686 patients with DME that was considered not immediately sight-threatening...
ruboxistaurin treatment did not significantly increase the time to a primary endpoint event. After 36 months, an endpoint event had occurred for 55% of patients in the placebo group and 55%, 53%, and 47% for the ruboxistaurin 4-, 16-, and 32-mg dose groups, respectively (P = .23). At the highest dose, ruboxistaurin was associated with lower rates of central DME and the development of moderate vision loss than placebo.

Other approaches that are currently being evaluated include inhibition of growth hormone and combining medical treatment with photocoagulation, although no studies that have examined these treatment strategies have been published.

PREVENTING VISION LOSS

The results of these studies demonstrate that several pharmacological treatment strategies may slow the progression of retinal injury and vision loss in patients with diabetes, especially the basic approaches to normalize blood glucose, BP, and serum cholesterol, which are effective in lowering all the secondary complications of diabetes. Preventing the progression of DR is particularly important because it is easier to prevent the progression of injury than to treat retinal injury once it has developed. Regular eye examinations are also important in preventing vision loss but are only performed in approximately 50% of patients with diabetes.29 An eye examination may actually help to prompt the patient to improve the management of his/her diabetes when the patient returns to their primary care physician, because one of the most significant health concerns for most people, along with heart disease and cancer, is blindness. For the general population, the risk of heart disease or cancer is much higher than the risk of blindness, but this is not true for patients with diabetes.

DIABETIC RETINOPATHY CLINICAL NETWORK

The National Eye Institute has recently begun an initiative to develop a network of clinical trial investigators and clinics to facilitate the clinical investigation of DR and DME. This effort is being coordinated by the National Eye Institute supported centers of the Diabetic Retinopathy Clinical Research Network (DRCR.net) including: the Coordinating Center in Tampa, the Reading Center at the University of Wisconsin, and the Chairman’s Office at the Joslin Clinic in Boston. It also includes industry collaboration, such as the development of a preservative-free steroid that is administered in a small injection volume (0.05 instead of 0.1 mL), reducing the risk of complications, such as the toxicity associated with the preservative or the increased intraocular pressure that can come after injection of 0.1 mL. A preservative-free steroid preparation is also being developed at the National Eye Institute. Although triamcinolone formulations that are currently available (eg, Kenalog) are relatively inexpensive, they contain benzyl alcohol as a preservative, which has been demonstrated to be toxic to the retina in animal experiments.24 Although it is possible that the steroid protects against the toxic effects of the preservative, it seems preferable to avoid the use of the preservative altogether if possible.

At present, there are more than 100 clinical centers in DRCR.net, and several studies are in progress. Enrollment has been completed in a study that is examining different approaches to laser treatment for DME photocoagulation, in order to define a standard of care for laser treatment. Although many clinicians report that they are using the ETDRS technique, there is considerable variation from investigator to investigator in exactly how the ETDRS techniques are implemented. This may be due in part to the fact that the participants in the ETDRS have changed their treatment methods over the years. For example, many clinicians use much lighter burns than were used 20 years ago. A trial of intravitreal triamcinolone using preservative-free prefilled syringes of 1 mg and 4 mg for 3 years has begun enrollment in several clinics. The 3-year results are most important because of the concerns related to the known complications of glaucoma and cataract formation, which cannot be adequately assessed in shorter trials.

The clinical research group is also conducting clinical trials to examine vitrectomy, beginning with a cohort study and with a possible controlled clinical trial to follow. Another study will examine whether patients will do better with peribulbar or retrobulbar steroids, and the use of combination therapy with steroids and photocoagulation. The network remains open to qualified clinical centers and clinicians who are interested in participating in clinical trials of the treatment of DME and who have the ability to perform OCT studies.
SUMMARY AND CONCLUSIONS

Laser photoocoagulation is often effective for the treatment of DR, but many patients do not exhibit significant improvement with currently available therapies. Pharmacologic treatments may provide alternative or adjunctive strategies to the treatment of DR. Randomized controlled clinical trials have demonstrated that intensive insulin therapy, BP control, and lipid lowering slow the progression of DR. Aldose reductase inhibition and antiplatelet therapy using aspirin were not effective in randomized trials. The development of DME is slowed by the effective management of blood glucose, BP, serum cholesterol; progression is slowed by laser treatment; and intravitreal steroid administration may help improve the overall prognosis in persons with vision loss from DME. New treatment options that are being evaluated in controlled clinical trials include inhibition of VEGF, growth hormone, and PKC. The DRCR.net will facilitate the conduct of large multicenter clinical trials of new treatments for DR.

REFERENCES

7. Aiello LP, Davis MD, Milton RC. Initial results of the protein kinase Cβ inhibitor diabetic macular edema study (PKC-DMES). Diabetologia. 2003;46(suppl 2):A42.