Exploratory Analysis of Diabetic Retinopathy Progression Through 3 Years in a Randomized Clinical Trial That Compares Intravitreal Triamcinolone Acetonide With Focal/Grid Photocoagulation

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Objective: To compare the effect of intravitreal triamcinolone acetonide with focal/grid photocoagulation on the progression of diabetic retinopathy.

Methods: We performed an exploratory analysis of participants with diabetic macular edema randomly assigned to receive laser therapy or intravitreal triamcinolone acetonide (1 or 4 mg). Fundus photographs were obtained at baseline and 1, 2, and 3 years. The main outcome measure was progression to proliferative diabetic retinopathy or worsening of 2 or more severity levels on reading-center masked assessment of 7-field fundus photographs, plus additional eyes that received panretinal photocoagulation or had a vitreous hemorrhage.

Results: From July 15, 2004, through May 5, 2006, 840 eyes from 693 participants were enrolled in the study and randomly assigned to receive laser therapy (n=330), 1 mg of triamcinolone acetonide (n=256), or 4 mg of triamcinolone acetonide (n=254). The cumulative probability of progression of retinopathy at 2 years was 31% (laser group), 29% (1-mg group), and 21% (4-mg group) (P=.64 in the 1-mg group and .005 in the 4-mg group compared with the laser group). These differences appeared to be sustained at 3 years.

Conclusions: Intravitreal triamcinolone acetonide (4 mg) appeared to reduce the risk of progression of diabetic retinopathy. Given the exploratory nature of this analysis and because intravitreal triamcinolone adverse effects include cataract formation and glaucoma, use of this treatment merely to reduce the rates of progression of proliferative diabetic retinopathy or worsening of the level of diabetic retinopathy does not seem warranted at this time.

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Progression of diabetic retinopathy, especially the development of proliferative diabetic retinopathy (PDR) with retinal neovascularization at the disc or elsewhere, can lead to severe visual loss and new-onset blindness from vitreous hemorrhage or traction detachment of the retina if left untreated. Despite advances in the treatment of both diabetes mellitus and diabetic retinopathy, in the United States alone there are approximately 700,000 persons with PDR, with 63,000 new cases of proliferative retinopathy and 5000 new cases of diabetes-induced legal blindness each year. The annual economic impact of retinopathy-associated morbidity in the United States, some of which is owing to PDR, is estimated to exceed $620 million.

Multicentered randomized clinical trials have demonstrated that glycemic control can reduce the risk of development of PDR. In addition, the Early Treatment Diabetic Retinopathy Study (ETDRS) has shown that treatment of high-risk PDR via panretinal photocoagulation (PRP) markedly reduces the rate of severe vision loss when comparing the clinical course of treated eyes with that of untreated eyes. The ETDRS demonstrated that PRP, applied when an eye nears or just reaches the threshold of high-risk PDR (having 3 or 4 high-risk characteristics), reduces the risk of severe vision loss to less than 4%. Although remarkably effective at reducing vision loss if applied in a timely and appropriate manner, the success of treatment depends on careful follow-up of eyes at risk for PDR so that PRP can be initiated promptly as an eye nears the thresh-
old of or develops high-risk PDR. Panretinal (scatter) photocoagulation is inherently destructive and is associated with adverse effects (such as, for example, macular edema with transient or permanent central visual loss or diminished peripheral visual loss9), potential complications from misdirected or excessive burns, and the progression of visual loss in nearly 5% of individuals despite appropriate treatment. Thus, identification of treatments other than glycemic control and PRP to reduce the risk of progression of retinopathy is desirable.

There is some rationale that supports a decision to consider whether corticosteroids could reduce the risk of progression of retinopathy, including the development of PDR. For example, corticosteroids have been shown experimentally to downregulate vascular endothelial growth factor production and possibly to reduce breakdown of the blood-retinal barrier. Similarly, steroids have been shown to have antiangiogenic properties, possibly because of attenuation of the effects of vascular endothelial growth factor.11,12 Furthermore, intravitreal triamcinolone acetonide has been used in the prevention of retinal neovascularization clinically13,14 and in animal studies.15,16

A randomized clinical trial15,16 by the Diabetic Retinopathy Clinical Research (DRCR) Network was designed to determine if 1 or 4 mg of intravitreal triamcinolone acetonide sodium phosphate could reduce the risk of visual acuity loss from diabetic macular edema compared with focal/grid photocoagulation. At 2 years of follow-up (the primary outcome visit for the trial), focal/grid photocoagulation was more effective with fewer adverse effects than the 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone acetonide in the treatment of diabetic macular edema. Progression of retinopathy was not the primary outcome in this trial, although change in retinopathy level was a planned secondary outcome. In addition, an exploratory analysis, as described herein, was undertaken to determine whether intravitreal triamcinolone as given in this trial might reduce the risk of progression of retinopathy for up to 3 years.

METHODS

The methods for the DRCR Network trial that compares intravitreal triamcinolone and focal/grid photocoagulation have been published in detail elsewhere15,16 with the complete protocol available online.17 In brief, eligible eyes were randomized to focal/grid photocoagulation, 1 mg of intravitreal preservative-free triamcinolone acetonide as often as every 4 months, or 4 mg of intravitreal preservative-free triamcinolone acetonide as often as every 4 months. Study eyes had diabetic macular edema with an optical coherence tomography central subfield thickness of at least 250 µm and a best-corrected visual acuity letter score of 73 (approximate Snellen equivalent 20/40) through 24 (approximate Snellen equivalent 20/320) after a protocol refraction and visual acuity measurement by means of an electronic visual acuity protocol.18 Study eyes could not have a history of PRP within 4 months before randomization or an anticipated need for PRP in the 4 months after randomization. Fundus photographs were obtained at baseline and annually to assess retinopathy level by masked graders.

During a planned periodic review of adverse events, the focal/grid photocoagulation–treated eyes were noted to have had a greater number of vitreous hemorrhage events than the eyes treated with 4 mg of triamcinolone acetonide. To explore if this was owing to an effect on retinopathy progression, we created a hierarchy to identify all cases that may have progressed up to 3 years after randomization. Specifically, progression of retinopathy up to either of these time points was defined as follows: (1) cases that progressed from non-PDR (NPDR) (level 53 or lower) to PDR (level 61 or higher) via reading-center grading of 7-field standard stereoscopic fundus photographs where no PDR (less than level 61) was identified at baseline, plus (2) additional cases that received PRP between baseline and follow-up (that were not identified in the first situation), plus (3) additional cases that had vitreous hemorrhage between baseline and follow-up (not already identified in the first 2 situations), plus (4) additional cases that worsened by 2 or more levels on the ETDRS diabetic retinopathy scale on reading-center grading of fundus photographs. All randomized eyes were included in the analyses, regardless of baseline retinopathy severity. Although eyes with PDR at baseline cannot meet the outcome by progression from NPDR to PDR, they can still meet the definition of progression per the PRP or vitreous hemorrhage criteria or by worsening of 2 or more retinopathy severity levels.

Cumulative probabilities of progression of retinopathy at each 4-month interval visit up to 36 months were calculated by means of the life-table method.19 Data from 116 eyes from participants who discontinued the study before 2 years without meeting the outcome definition were censored in the interval after the last completed visit from those participants. After analysis of the 2-year primary outcome data, the trial was stopped. Therefore, not every participant had the potential to complete post–2-year follow-up. Data from an additional 285 eyes, from participants who discontinued the study in the third year without meeting the outcome definition, were censored before the 3-year mark (from 265 eyes that did not have the potential to complete 3 years of follow-up and 20 that did). If photographic data were missing (because of noncompletion or nongradable images), then the outcome definition depended solely on PRP and vitreous hemorrhage criteria. If neither of these was met, it was assumed the eye would not meet photographic criteria either and it was considered “no event” for the purposes of the study. There were 66 eyes from participants who completed 3 years of follow-up, did not have PRP or vitreous hemorrhage, and had missing photographic data, which potentially could have been an event. The proportional hazards model was used to compare treatment groups, with adjustment for baseline visual acuity, history of prior focal/grid photocoagulation, and baseline retinopathy severity. No substantial deviations from the proportional hazards assumption were detected. A robust sandwich estimate of the covariance matrix was used to account for correlation within participants who had both eyes studied.16 All reported P values are 2-sided. Statistical analyses were conducted by means of SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

From July 15, 2004, through May 5, 2006, 840 eyes from 693 participants were enrolled in the study and randomly assigned to receive laser therapy (n=330), 1 mg of triamcinolone acetonide (n=256), or 4 mg of triamcinolone acetonide (n=254). Of those participants, 95% had type 2 diabetes and 49% were women; the mean age of participants was 63 years. Of the total eyes,
73% had NPDR, 27% had PDR on reading-center grading of baseline fundus photographs, and 16% had previous PRP. Characteristics were similar among treatment groups.

The cumulative probability of progression of retinopathy in the laser group, 1-mg group, and 4-mg group up to 1 year was 21%, 19%, and 14%, up to 2 years was 31%, 29%, and 21%, and up to 3 years was 37%, 35%, and 30%, respectively (at 1 year, \( P = .71 \), \( P = .03 \), and \( P = .08 \); at 2 years, \( P = .64 \), \( P = .005 \), and \( P = .03 \); and at 3 years, \( P = .73 \), \( P = .02 \), and \( P = .07 \) in comparison among the laser and 1-mg group, the laser and 4-mg groups, and the 1-mg and 4-mg groups, respectively; Figure).

Progression of retinopathy partitioned into a stepwise hierarchy of criteria to meet the outcome definition or treatment of each criterion as a separate outcome measure produced similar trends, although to a lesser degree than the combined definition (Table). The cumulative probability of progression of retinopathy was smaller in the 4-mg group than in the laser and 1-mg groups up to 1, 2, and 3 years within every level of subgroup evaluated (data not shown) with respect to level of retinopathy at baseline (NPDR vs PDR), pseudophakic status at baseline, and number of randomized treatments received.

There were 72 participants who had 1 eye assigned to the laser group and the other assigned to the 1 mg of triamcinolone acetonide group and 75 participants who had 1 eye assigned to the laser group and the other assigned to the 4 mg of triamcinolone acetonide group. For the participants in the laser and 1-mg groups, 13% met the definition of progression of retinopathy by 3 years in the laser-group eye but not in the 1-mg-group eye, and 17% met the definition in the 1-mg-group eye but not in the laser-group eye. For the participants in the laser and 4-mg groups, 21% met the definition by 3 years in the laser-group eye but not in the 4-mg-group eye, compared with 7% in the 4-mg-group eye but not in the laser-group eye.

This exploratory analysis suggests that 4 mg of intravitreal triamcinolone acetonide as given in this trial can reduce the risk of progression of retinopathy for a 3-year period. The effect was sustained between years 1 and 2 and again between years 2 and 3, even though most eyes did not receive corticosteroids every 4 months in the second year and less than 50% received any corticosteroids in the third year. Theoretically, it is possible the reduction in risk of retinopathy progression may have been even greater if intravitreal triamcinolone had been given more frequently between years 1 and 3 of follow-up. On the other hand, it is possible that eyes with less severe or resolved edema may have had injections discontinued, and such eyes may have been healthier and thus did not have progression of diabetic retinopathy at a faster rate in the absence of additional injections.

It is unlikely that the observed difference between the 4 mg of triamcinolone acetonide group and the focal/grid photocoagulation group is attributable to an increase in retinopathy progression caused by focal/grid photocoagulation. On the basis of data from the ETDRS, there does not appear to be a difference in risk.
of development of PDR in eyes with mild-to-severe NPDR between focally treated eyes and untreated eyes (11.1% in the group assigned to immediate focal/grid photocoagulation and 10.8% in the group assigned to deferred focal/grid photocoagulation at 1 year [Frederick L. Ferris, MD, written communication, November 21, 2008]). In addition, the fact that the cumulative incidence in the laser group and the 1 mg of intravitreal triamcinolone acetonide group appeared similar, even though most eyes in the 1-mg group did not receive focal/grid photocoagulation, provides further evidence to suggest it is unlikely that the 4-mg effect resulted from an increased risk of progression of retinopathy in the laser group.

Although there are numerous basic scientific findings to support the hypothesis that anti-inflammatory medications, such as corticosteroids, could reduce the risk of ocular progression toward the threshold of PDR,20-23 there are limited data to support this hypothesis from the clinical trial literature. A similar finding was observed in a trial that evaluated the effect of sustained-release fluocinolone acetonide intravitreal implants with regard to diabetic retinopathy levels in participants with diabetic macular edema in which 197 participants were randomized to receive either a 0.59-mg fluocinolone acetonide implant or standard of care (additional laser treatment or observation).24 There was a higher rate of improvement and a lower rate of worsening in diabetic retinopathy severity in the fluocinolone acetonide implant group than in the standard-of-care group (\(P<.001\) at 6 months, \(P<.002\) at 1 year, \(P=.01\) at 2 years, and \(P<.02\) at 3 years after implantation) (P. Andrew Pearson, MD, written communication, November 17, 2008).

Some of the strengths of the current investigation include the prospective collection of fundus photographic and treatment data and randomization by treatment group. Analyses of the fundus photographs were completed by reading-center graders, who provided uniform assessment across 88 clinical sites from which the data were obtained. The graders also were masked to treatment assignment. In addition, during the evaluation of the subgroup of participants who had 1 eye enrolled in the laser group and the other in the 4-mg triamcinolone acetonide group, presumably controlling for the effect of systemic factors on progression to PDR, similar outcomes in favor of the 4-mg group reducing the risk of progression to PDR were noted.
This study has a number of potential weaknesses. Its protocol was not designed primarily to determine the effect of intravitreal corticosteroids on prevention of the progression of retinopathy, and the analyses presented were not planned secondary outcomes before the onset of the study, although the concept was considered because the analysis plan at the onset of the study included comparison among the change in retinopathy levels on fundus photographs. Also, data from approximately 14% of participants were censored before the 2-year visit and the same was true for an additional 34% between the 2- and 3-year visits (of which only 7% had the potential to complete the 3-year visit because the study was closed early). Furthermore, interpretation of these results should be tempered by the recognition that the 4-mg triamcinolone-acetonide group was more likely to have cataract (31% and 64% of phakic eyes had a cataract extraction by 2 and 3 years, respectively, in the 4-mg group, compared with 23% and 35%, respectively, in the 1-mg group and 13% and 21%, respectively, in the laser group). The cataract could obscure identification of PDR by the reading center or by the treating ophthalmologist, which would result in less likelihood to proceed with PRP. However, this possibility seems unlikely because the view through most cataract, at the time of surgery, is usually sufficient to identify PDR by retina specialists. Also, development of cataract, depending on its severity, is not likely to influence perception of vitreous hemorrhage by a participant or identification of vitreous hemorrhage by the treating ophthalmologist. Also, failure to identify PDR by the ophthalmologist potentially should have increased the possibility of vitreous hemorrhage events from untreated (unrecognized) PDR. However, the observed proportion with vitreous hemorrhage was less in the 4-mg group than in the focal/grid photocoagulation group. Finally, the investigators were not masked with respect to whether the participant received intravitreal triamcinolone or focal/grid photocoagulation, and 2 of the 4 components of the primary outcome for this analysis were determined by the investigator; however, investigators were masked to the dose of triamcinolone.

Use of this intravitreal corticosteroid preparation to reduce the likelihood of progression of retinopathy is not warranted at this time because of the increased risk of glaucoma and cataract associated with intravitreal steroid use. Any treatment to be used routinely to prevent PDR likely needs to be relatively safe because the condition already can be treated successfully and safely with PRP. Nevertheless, further investigation with regard to the role of pharmacotherapy for reduction of the incidence of progression of retinopathy appears to be warranted.

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Group Information: A published list of the DRCR Network investigators and staff who participated in this protocol can be found in Ophthalmology. 2008;115(9):1447-1449, with a current list available at http://public.drcr.net/DRCRnetstudies/studies/myInvestigators.php.

REFERENCES

12. Penfold PL, Gyory JF, Hunyor AB, Billson FA. Exudative macular degeneration