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Patients With Good Vision and Diabetic Macular Edema Involving the Center of the Macula:

To Treat or Not to Treat?

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Diabetic retinopathy is the leading cause of blindness and visual impairment in the working-age population in the United States and worldwide.[1] Diabetic macular edema, a vision-threatening form of diabetic retinopathy, is the swelling or thickening of the retina at the macula, the structure that is responsible for the highest resolution of vision. Diabetic macular edema may occur in any stage of diabetic retinopathy, ranging from minimal diabetic retinopathy to severe proliferative diabetic retinopathy, which is the other form of vision-threatening diabetic retinopathy.

From 1985 to 2010, the standard of therapy for diabetic macular edema was focal (used to treat focal macular edema) or grid (used to treat diffuse macular edema) laser photocoagulation. In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) of laser photocoagulation for the treatment of diabetic macular edema in 1122 patients (with 2224 affected eyes; 754 randomized to focal/grid laser and 1490 deferral of laser) demonstrated reduction in the risk of moderate vision loss of 3 lines of vision (as assessed by best corrected visual acuity following refraction) by about 50%,[2] whereas the more extensive scatter laser photocoagulation applied to the severe form of disease, proliferative diabetic retinopathy, resulted in about 90% reduction of severe vision loss.[3] Laser photocoagulation was the mainstay of therapy for decades until the introduction of intraocular injections of anti-vascular endothelial growth factor (VEGF) agents for the treatment of diabetic retinopathy. The use of intravitreous anti-VEGF therapies for retinovascular diseases, such as diabetic retinopathy, is a profound development that revolutionized the management of ocular diseases.

Pivotal clinical trials of intravitreous injections of anti-VEGF agents in eyes with diabetic macular edema and impaired vision demonstrated better visual acuity when compared with focal/grid laser therapy.[4–7] Improvements in the severity of diabetic retinopathy also occurred with intravitreous anti-VEGF therapies.[8,9] The 3 available anti-VEGF agents

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include bevacizumab, ranibizumab, and aflibercept. The use of anti-VEGF therapy was facilitated by the development of optical coherence tomography (OCT), which is a non-invasive form of high-resolution imaging using low coherence interferometry to measure the retinal thickness, both qualitatively and quantitatively.

The Diabetic Retinopathy Clinical Research (DRCR) Retina Network, a clinical network supported by the National Eye Institute, National Institutes of Health, conducted seminal randomized clinical trials that have provided level 1 evidence to establish guidelines for the treatment of patients with diabetic retinopathy. In 2010, the DRCR conducted a randomized trial that compared therapies including intravitreous ranibizumab, intravitreous steroids, and focal/grid laser photocoagulation in 854 eyes (in 691 patients) with diabetic macular edema and impaired visual acuity.[4] The results showed superior visual acuity with intravitreous ranibizumab, with 50% of eyes gaining 2 lines of visual acuity and 30% gaining 3 lines at 1 year. Similarly, the DRCR compared the 3 anti-VEGF agents in 660 eyes (in 660 patients) with diabetic macular edema and moderately to severely impaired vision.[10] The initial results at 1 year showed no differences between the 3 treatment groups with mild baseline visual impairment, although aflibercept was more effective than the other 2 agents for those eyes with more severe visual impairment (20/50 to 20/320).[10] However, at 2 years, aflibercept was no longer more effective than ranibizumab for the treatment of eyes with diabetic macular edema and more severe visual impairment.[11]

In this issue of *JAMA*,[12] the DRCR Retina Network investigators report on another randomized clinical trial designed to evaluate 3 treatment strategies for 702 eyes (among 702 patients) with diabetic macular edema that involved the center of the macula but with good visual acuity (20/25 or better). There are limited data on the management of such eyes, and a large proportion of patients who present clinically with diabetic macular edema have good visual acuity. Approximately 40% of patients who presented with diabetic macular edema for the laser treatment trials in the ETDRS had visual acuity of 20/20 or better, and 45% were between 20/25 and 20/40 at baseline.[13]

In the current study,[12] participants with diabetic macular edema and good visual acuity were randomly assigned equally to 3 treatment strategies that were initiated with intravitreous injection of aflibercept (2.0 mg) (n = 226), laser photocoagulation (n = 240), or observation (n = 236) and followed up for 2 years. Those who were randomly assigned to intravitreous aflibercept received injections every 4 weeks as needed depending on visual acuity and OCT-measured retinal thickness. Participants in the laser photocoagulation group received the therapy every 13 weeks, and patients in the observation group received no therapy initially. However, when visual acuity decreased by 1 eye chart line on 2 consecutive visits or by 2 lines at 1 visit, aflibercept injections were initiated in the laser and observation groups. The study evaluated a strategy of immediate anti-VEGF therapy vs waiting for a threshold of decreased visual acuity before starting anti-VEGF therapy.

No statistically significant differences were seen among the 3 treatment groups in the primary outcome, which was the proportion of participants who experienced decreased visual acuity of 5 or more letters from baseline: aflibercept (16%), laser photocoagulation (17%), and observation (19%). Mean visual acuity at 2 years was about 20/20 in all 3

treatment groups, and the proportion of eyes that had 20/20 visual acuity at year 2 were 77% in the aflibercept group, 71% in the laser group, and 66% in the observation group. Comparison of the aflibercept-treated group with photocoagulation revealed a relative risk of 1.11 (95% CI, 0.97–1.27, $P = .15$) while the comparison of aflibercept with observation resulted in a relative risk of 1.18 (95% CI, 1.01–1.37; $P = .03$). The cumulative probabilities of receiving aflibercept in the laser and observation groups were 26% and 36%, respectively. No cases of endophthalmitis, a potential adverse effect of intraocular injection, developed following intravitreal injection. In addition, the rate of cardiovascular or cerebrovascular adverse events was not significantly different among the 3 treatment groups (7% aflibercept, 5% laser, 3% observation; $P = .28$).

This is an important study because of the public health implications for the treatment of the millions of patients with diabetic macular edema, who often present with good vision. Although no previous study has evaluated the treatment strategies for eyes with good vision and diabetic macular edema involving the center of the macula, clinicians have applied results from previous studies involving eyes with impaired vision vs eyes with good vision. The current data demonstrated that these 3 treatment strategies—anti-VEGF therapy, laser, or observation—resulted in no difference in risk of vision loss at 24 months and showed no harm to visual function while waiting to initiate anti-VEGF therapy only if there are clinically meaningful changes in visual acuity on follow-up. In fact, 74% of the laser group and 64% of the observation group did not require aflibercept injections during the 2 years. This strategy of delaying aflibercept therapy unless visual acuity decreases could save on health care costs because the anti-VEGF therapies are expensive. It has been estimated that from 2011 to 2015, ranibizumab and aflibercept accounted for 12% of the Medicare Part B drug claim spending.[14] Previous studies conducted by the DRCR suggested that in eyes with diabetic macular edema with mild visual impairment, the 3 anti-VEGF agents performed equally effectively.[10] In these with eyes with good vision, it would be reasonable to assume that all 3 anti-VEGF agents would also be equivalent.

It is the patient who has the most to gain from these study results. Some patients may not need intraocular injections of anti-VEGF therapies, which carry a risk, albeit small, of endophthalmitis. The cost of the drugs as well as the monetary cost associated with increased frequency of eye examinations associated with anti-VEGF therapies would be avoided. This approach could not only reduce the increased economic burden associated with intraocular injection therapy, but also could reduce the demands and psychological burden of treatment for diabetic retinopathy for the patients, their families, and society.

Despite the availability of therapies for diabetic retinopathy, it is imperative that clinicians educate patients about the importance of medical therapies including tight glycemic control and blood pressure control as well as appropriate treatment of dyslipidemia in reducing the risk of development and progression of diabetic retinopathy and other microvascular complications.[15,16] The volunteers who participated in these clinical trials maintained reasonably good hemoglobin A_{1C} levels. Treating physicians need to consider the generalizability of the study results to their patients and the individual patient's medical status. These treatment strategies for diabetic macular edema for eyes with good vision also depend on the continued adherence of patients, who have numerous comorbidities, to their

follow-up. Treating physicians will need to judiciously determine the best treatment option for their patients with diabetic macular edema and good vision. Once again, the DRCR Retina Network has provided valid level 1 evidence to guide physicians whether (and how) to treat or not to treat persons with diabetic retinopathy, including those with good visual acuity.

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