Macular edema is a common cause of vision loss in patients with diabetes. Chronic elevation of serum glucose levels leads to capillary damage that results in microaneurysm formation in the retina. Leakage from these microaneurysms leads to vision loss if the fluid involves the center of the fovea. The mainstay of therapy for more than 25 years was focal laser photocoagulation applied to or near the microaneurysms. However, results from clinical trials of drugs that block vascular endothelial growth factor (VEGF) for the treatment of diabetic macular edema have led to a dramatic shift away from laser therapy to primary treatment with intravitreal injections of one of three anti-VEGF drugs: aflibercept, bevacizumab, and ranibizumab.

Researchers from the Diabetic Retinopathy Clinical Research Network now report in the Journal findings from a comparative trial of drugs to treat diabetic macular edema. Although each of the three drugs produced substantial improvement in visual acuity at 1 year, there were important differences in treatment effects in pre-specified subgroups. In eyes with visual acuity of 20/40 or better, there was no difference among the drugs in improvement in the visual-acuity letter score (mean improvement, 8 for each drug) or the number of injections (median, 9 for each drug) required to achieve this result. However, in eyes with visual acuity of 20/50 or worse, there was a clear advantage with aflibercept in improvement in the visual-acuity letter score (mean improvement, 19) over bevacizumab (mean improvement, 12) or ranibizumab (mean improvement, 14), although the number of injections was similar among aflibercept (median, 10), bevacizumab (median, 11), and ranibizumab (median, 10).

For the entire study sample, improvement in the visual-acuity letter score was greater by 2 to 3 with aflibercept than with the other two agents. However, with a highly significant interaction between baseline visual acuity and treatment effects, the overall results do not apply to patients in either subgroup.

Aflibercept and ranibizumab reduced retinal thickness more than bevacizumab in both visual-acuity subgroups, but the anatomical benefit translated into a visual-acuity benefit only in eyes with a baseline visual acuity of 20/50 or worse. The greater reduction in retinal thickness with aflibercept is consistent with the lower rate of supplemental laser treatment required in aflibercept-treated eyes than in eyes treated with the other agents.

There were no significant differences in safety observed among the drugs, although in a post hoc analysis, there were more cardiovascular events in patients treated with ranibizumab (37 patients, 17%) than in those treated with aflibercept (20 patients, 9%) or bevacizumab (19 patients, 9%) (P=0.01). Given the absence of differences in cardiovascular safety observed in other trials of diabetic macular edema, as well as the absence of consistent differences in cardiovascular safety in comparative trials of these drugs for the treatment of age-related macular degeneration, we agree with the authors that the difference may have been due to chance and that the topic warrants continued surveillance.

Approximately 75% of patients with diabetic macular edema in the general population present with a visual acuity of 20/40 or better. Because there were no significant differences in safety or efficacy among drugs in patients with this presenting visual acuity, cost becomes a major consideration in choosing therapy. Given the large difference in cost to patients per dose among bevacizumab ($50), ranibizumab ($1,200), and aflibercept ($180),
and aflibercept ($1,950), bevacizumab should be considered as first-line therapy in patients with a visual acuity of 20/40 or better.

For patients who present with a visual acuity of 20/50 or worse, improvement in vision was greatest with aflibercept and similar between bevacizumab and ranibizumab. Aflibercept should be considered as first-line therapy in these patients, with bevacizumab as the alternative given the lack of a significant difference in visual outcome between bevacizumab and ranibizumab and the large difference in cost between the two drugs. The equivalence of bevacizumab and ranibizumab in effects on visual acuity has now been shown in different disease states, including diabetic macular edema in the current trial and neovascular age-related macular degeneration in several multicenter clinical trials.5-9

There are powerful forces in addition to efficacy and safety that affect drug selection by physicians. These include the current requirement for a patient-specific prescription, which limits or delays access to compounded bevacizumab in some states; the rebates paid directly to physicians from pharmaceutical companies to reward use of a more expensive drug; and the policy of the Centers for Medicare and Medicaid Services to reimburse on the basis of a percentage of the cost of a drug, so that the agency provides higher payments to physicians when more expensive drugs are prescribed. We believe that all financial incentives and logistic barriers to providing the least expensive drug, among drugs equivalent in safety and efficacy, should be eliminated so that patients may benefit fully from the results of this Diabetic Retinopathy Clinical Research Network trial as well as those from other comparative trials.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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