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Comparative Effectiveness Trial for Diabetic Macular Edema: Three Comparisons for the Price of One Study

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Thickening of the center of the retina from diabetes, diabetic macular edema (DME), is a common cause of vision impairment and blindness in the U.S.¹ DME is associated with increased intraocular levels of vascular endothelial growth factor (VEGF).² VEGF also can cause proliferation of new vasculature on the surface of the retina (neovascularization of the disc or elsewhere), termed proliferative diabetic retinopathy (PDR). Left untreated, DME or PDR may damage the retina, causing substantial vision loss.

Recently, anti-VEGF agents injected into the vitreous have replaced macular laser photocoagulation as the preferred initial treatment for DME.³ Anti-VEGF agents for DME include aflibercept (EYLEA®, Regeneron Pharmaceuticals, Inc.), bevacizumab (Avastin®, Genentech), and ranibizumab (Lucentis®, Genentech). Although all three are used to treat DME, ophthalmologists had little evidence regarding their relative efficacy and safety. The paucity of comparative effectiveness data of these agents for DME and the large differences in their costs justified treatment comparison studies. Medicare allowable charges in 2014 were \$1961 for aflibercept (2.0-mg/0.05 mL), \$67 for bevacizumab (assuming 10-mg used for repackaging a 1.25-mg injection/0.05 mL), and \$1189 for ranibizumab (0.3-mg/0.05 mL). Considering a prior clinical trial reported a median of 17 ranibizumab injections for DME over 5 years, including 13 in the first year,^{4,5} costs might be reduced if bevacizumab was equally safe and effective.

The Diabetic Retinopathy Clinical Research Network ([DRCR.net](http://www.drcr.net)), an NIH-sponsored network dedicated to diabetic eye disease research, compared the effectiveness of aflibercept to bevacizumab, aflibercept to ranibizumab, and ranibizumab to bevacizumab in a

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Additional Contributions: Regeneron Pharmaceutical provided the aflibercept and Genentech provided the ranibizumab for the study. Genentech also provided funding for blood pressure cuffs and the collection of serum and urine that are not part of the main study results reported herein. As per the [DRCR.net](http://www.drcr.net) Industry Collaboration Guidelines (available at www.drcr.net), the [DRCR.net](http://www.drcr.net) had complete control over the design of the protocol, ownership of the data, and all editorial content of presentations and publications related to the protocol.

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randomized clinical trial at 89 sites of 660 patients with DME causing vision loss. Approximately one-third were treated with aflibercept, bevacizumab, or ranibizumab following a standardized treatment protocol.

The primary outcome was mean visual acuity change from baseline to one year. All three treatment groups had improvement at one month with substantial improvement at one year.⁶ In each group, <2% had substantial vision loss. Overall, treatment with aflibercept resulted in statistically greater average improvements in vision compared with bevacizumab or ranibizumab. However, a significant interaction between treatment group and baseline visual acuity showed that the worse the initial visual acuity, the greater the relative advantage of aflibercept over the other two agents for both visual acuity and retinal thickness. In eyes with an initial visual acuity Snellen equivalent of 20/32 to 20/40, about half the study eyes, a clinically relevant advantage of aflibercept over bevacizumab or ranibizumab on average change in visual acuity was not seen. In eyes with initial visual acuities of 20/50 or worse, aflibercept had a greater mean improvement in vision than bevacizumab or ranibizumab. Irrespective of starting visual acuity, bevacizumab's effects on average macular edema reduction were less than those of the other two agents. No differences were identified among the three groups in death rates, serious adverse events, hospitalization, or pre-specified systemic adverse events.

These results are based on the [DRCR.net](#) DME treatment algorithm, including an initial series of 6 monthly injections for most eyes. Injections continue monthly thereafter provided the vision or optical coherence tomography (OCT) central subfield thickness (CST) of the macula is improving. Injections are deferred once the vision and thickness stabilize (<5 letter or <10% CST change) following two consecutive injections. Treatment is resumed if vision or CST worsens. After 6 months, if DME persists and is not improving, macular (focal/grid) photocoagulation is added.

Reconciling the Primary Outcome vs. Visual Acuity Subgroup Analyses

Why did the [DRCR.net](#) investigators emphasize visual acuity subgroup analyses when the primary outcome was the overall cohort? The magnitude of the difference in the overall primary analysis (all eyes) is not relevant to clinical decisions in the presence of a strong interaction with initial visual acuity ($P<0.001$).⁶ This is particularly true when there is biologic plausibility for the interaction which was anticipated and documented prior to initiating this trial. Specifically, investigators hypothesized *a priori* (documented in the statistical analysis plan) that eyes with lower visual acuity might have higher VEGF levels on average, resulting in a larger relative treatment benefit for the anti-VEGF agent with the stronger VEGF-binding affinity, thought to be aflibercept. Given the strong interaction subsequently identified between treatment group and baseline visual acuity, investigators concluded that the overall mean visual acuity change (all eyes) under-represents the relative benefit of aflibercept in worse-seeing eyes and over-represents the relative effect of aflibercept in better-seeing eyes. Therefore, the overall effect does not have clinical relevance because it does not apply to either better- or worse-seeing eyes. This view is consistent with epidemiologic dogma that an overall analysis is not meaningful when there is a strong interaction believed to be true.

Are Mean Changes Clinically Relevant?

The primary outcome in this trial was the mean difference in visual acuity change from baseline to 1 year. Since visual acuity is measured as a continuous letter score from 100 (Snellen equivalent 20/10) to 0 (Snellen equivalent 20/800), mean change in letter score often is an excellent summary statistic of visual acuity change over time for a group of eyes. However, given that average change is describing a shift in a distribution and not a change on an individual patient level, average change in letter score can be difficult to translate into clinical relevance. On the other hand, a change of a letter score of at least 15 (3 lines on an eye chart, representing a doubling in the visual angle [size of the letters]) commonly is used to indicate clinically relevant changes for a patient.⁷ To appreciate how mean changes in distribution relate to percentages of eyes with meaningful changes in this [DRCR.net](#) trial, note that the worse visual acuity subgroup at baseline had mean changes in visual acuity letter score at 1 year of +18.9, +11.8, and +14.2, in the aflibercept, bevacizumab, and ranibizumab groups respectively. This +6.5 letter mean difference adjusted for baseline vision (95% confidence interval [CI]: 2.9–10.1, $P=0.001$) between aflibercept- and bevacizumab-treated groups equates on a patient level to 63% more aflibercept-treated eyes than bevacizumab-treated eyes improving at least 15 letters (observed improvement, 67% vs. 41%, $P<0.001$). Similarly, the +4.7 letter mean difference, adjusted for baseline vision, (95% CI: 1.4–8.0, $P=0.003$) between aflibercept- and ranibizumab-treated groups equates to 34% more aflibercept-treated eyes than ranibizumab-treated eyes improving 15 letters (observed improvement, 67% vs. 50%, $P=0.008$). Most ophthalmologists would judge these mean letter score differences as clinically relevant.

One-year Conclusions

At one year, substantial improvement in visual acuity occurred with all three treatment groups. Many factors are important when choosing an anti-VEGF agent for DME including efficacy, safety, price, and specifically for bevacizumab, availability of reliable and safe repackaging (compounding). The [DRCR.net](#) comparative effectiveness trial provides reliable data regarding efficacy and safety through one year.⁶ With availability of quality repackaging, when an individual patient does not have access to aflibercept or ranibizumab, initiating treatment with bevacizumab is a reasonable strategy. With better initial vision, ophthalmologists should consider that no differences in vision outcomes, on average, were identified in the [DRCR.net](#) 1-year report among any of the three anti-VEGF agents,⁶ recognizing there was less macular thinning with bevacizumab than the other agents. In situations where an individual has access to aflibercept to treat DME, the worse the vision, the greater the reason for an ophthalmologist to consider using that agent.

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