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DRCR.net Protocol T: Relative Effect of Anti-VEGF Agents Depended on Baseline Visual Acuity

In the much-anticipated DRCR.net Protocol T study, treatment with aflibercept (Eylea, Regeneron) yielded greater improvement in visual acuity than ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech) among patients with center-involved diabetic macular edema (DME).[1] However, according to the study's authors, the difference in outcome was "not clinically meaningful, because the difference was driven by the eyes with worse visual acuity at baseline ($P < .001$ for interaction)."

After 1-year of follow-up, patients in the aflibercept group gained 13.3 letters, compared with 11.2 letters in the ranibizumab group (P = .03 vs aflibercept) and 9.7 letters in the bevacizumab group (P < .001 vs aflibercept). There were no statistically significant differences among subgroups of patients starting the trial with visual acuity between 20/32 and 20/40 (between 78 and 69 letter score): 8.0 letters, 8.3 letters, and 7.5 letters in the aflibercept, ranibizumab, and bevacizumab groups, respectively.

However, there were statistically significant differences among patients who began the trial with 20/50 or worse vision (letter score < 69). There was a 18.9 letter gain in the aflibercept group; a 14.2 letter gain in the ranibizumab group ($P = .003$ versus aflibercept); and an 11.8 letter gain at the end of the trial in the bevacizumab group ($P < .001$ versus aflibercept).

According to the study authors, "there were no significant differences among the study groups in the rates of serious adverse events ($P = .40$), hospitalization ($P = .51$), death ($P = .72$), or major cardiovascular events ($P = .56$)."

REACTION

Retina Today reached out to officials from Regeneron and Genentech for reaction to the study results.

"We really couldn't have been happier with the results we saw initially, that in the overall population aflibercept was significantly better than bevacizumab and ranibizumab in the mean change in the overall [BCVA] over time, and that was the primary endpoint," said Robert Vitti, MD, MBA, vice president of clinical sciences ophthalmology, at Regeneron.

"When [the investigators] looked at the prespecified subgroups, that is, patients worse than 20/40 vision … then the differences among the three drugs were that much more stark," he said.

Officials with Genentech agreed with the study authors' interpretation that differences seen in the overall population may not be clinically significant.

"The majority of people with DME in the real world, 75% or so, have less severe vision loss—20/40 vision or better when they are diagnosed with DME. The study showed that [ranibizumab] is comparable to aflibercept in that group of people," said Jason Ehrlich, MD, group medical director, ophthalmology, at Genentech.

Further, Dr. Ehrlich said, the investigators noted that these differences in the overall population were largely driven by changes observed in the subgroup of patients with worse baseline visual acuity.

"There was a difference observed between [ranibizumab] and aflibercept in people with vision loss, and in particular in patients with the worst vision loss, so 20/100 or worse. That has not been seen in other studies, and we feel that needs additional evaluation," Dr. Ehrlich said.

It is also unknown whether baseline characteristics may have affected the study results. The DRCR.net has so far released demographic information only for the entire study population.

"When you are looking at subgroups, and you are seeing results that are happening for the first time, I think it is important to realize there may be reasons that are contributing to that: baseline characteristics, for example. We look forward to learning more about that in the future as we see the individual level data from the study," Dr. Ehrlich said.

INTERPRETATION AND POTENTIAL CLINICAL IMPACT

In an accompanying editorial commenting on the study, Daniel F. Martin, MD, of the Cole Eye Institute, and Maureen G. Maguire, PhD, of the University of Pennsylvania, said that, because of the comparable outcomes in the overall population, physicians should consider the cost of treatment when choosing an appropriate agent for patients.[2]

According to Drs. Martin and Maguire, among the largest segment of patients with DME presenting to retina specialists for treatment—those with 20/40 or better visual acuity—bevacizumab should be considered as first-line therapy.

"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 significant difference in visual outcome between bevacizumab and ranibizumab and the large difference in cost between the two drugs," Drs. Martin and Maguire wrote.

Several sources that *Retina Today* spoke to for this article stressed that extrapolating results from this study regarding bevacizumab may be problematic. Although the respective manufacturers supplied doses of aflibercept and ranibizumab, the bevacizumab used in the study was repackaged by a central pharmacy and underwent testing for sterility, purity, and potency before use, measures that may not be feasible in clinical practice. This fact was acknowledged by the study's authors, who also said that "lower-than-expected concentrations of bevacizumab in products obtained from pharmacies have been reported, although the potential effect on treatment outcome is unknown."

Also noted by the study authors was that "the effect of bevacizumab on reducing macular edema was less than that of the other two agents in both initial-visual-acuity groups [20/32 to 20/40 and 20/50 or worse]."

Another factor that may have affected outcomes was the differences in dosing regimens used by the study investigators. Doses were administered as often as every 4 weeks, but, per protocol, intravitreal injections were more often introduced on an as-needed (PRN) basis. According to the study protocol, drugs were to be injected every 4 weeks unless visual acuity was 20/20 or better with central subfield thickness below the eligibility threshold as defined by the study protocol and there was no change in response to treatment for the past two injections. After 24 weeks of follow-up, regardless of the visual acuity or central subfield thickness, an injection was withheld if there was no change in anatomy or visual acuity over two consecutive injections, but "treatment was reinitiated if the visual-acuity letter score or central subfield thickness worsened."

According to a source who spoke with *Retina Today*, the Protocol T study was the first time ranibizumab was used in a clinical trial for DME in a PRN fashion; ranibizumab is approved by the US Food and Drug Administration (FDA) for monthly use in patients with DME.

Overall, the results of the Protocol T study demonstrated a treatment benefit with anti-VEGF therapy among patients with DME. Still, although the study investigators "could not identify evidence of confounding or bias to explain the results," clinicians may want to note the following important caveats about the study before applying them to regular clinical practice.

"In this comparative-effectiveness, randomized clinical trial of center-involved diabetic macular edema causing decreased visual acuity, treatment with intravitreous aflibercept, bevacizumab, or ranibizumab was associated with a substantial improvement in mean visual acuity by 1 month, with the improvement sustained through 1 year with the use of a standardized retreatment protocol," the study authors wrote.

"When applying the results of this study to clinical practice, one should consider the eligibility criteria for this study, such as visual acuity, retinal thickness, and prior treatment for diabetic macular edema. The results may not apply to eyes with persistent or recurrent diabetic macular edema that are already being treated with anti-VEGF agents," the authors wrote.

1. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema [published online ahead of print February 18, 2015]. *N Engl J Med*. doi:10.1056/NEJMoa1414264.
2. Martin DF, Maguire MG. Treatment choice for diabetic macular edema [published online ahead of print February 18, 2015]. *N Engl J Med*. doi:10.1056/NEJMe1500351.

FDA Approved Ranibizumab for DR in the Presence of DME

The FDA has approved ranibizumab for use in patients with diabetic retinopathy (DR) in the presence of DME. Meanwhile, Regeneron, maker of aflibercept, has applied for and has been granted a supplemental biologics license application for the same indication.

The expanded approval for ranibizumab is for a 0.3 mg dose. According to information from the FDA, the drug's safety and efficacy in this indication were established in two clinical trials that demonstrated improvement in the severity of their DR in treated patients.

There were previously no approved medications for the treatment of DR, according to Genentech.

According to Regeneron, the target date of action for an expansion of aflibercept is March 30. In September 2014, the FDA granted aflibercept a breakthrough therapy designation for DR in patients with DME.

Nikon to Buy Optos

Nikon announced in a press release its intention to buy Optos.

Under the terms of the transaction , Optos shareholders will be entitled to receive 340 pence (US$0.52). The transaction values the entire issued and to be issued share capital of Optos at approximately £259.3 million (US$400.3 million).

The Optos directors intend to recommend unanimously that Optos shareholders vote in favor of the transaction, according to a press release. ■