Anti-PDGF Combination Therapy for AMD

Results of a phase 2 study.

BY RICHARD S. KAISER, MD

Patients with age-related macular degeneration (AMD) lose vision for several reasons. Photoreceptor degeneration is a key contributing factor in both dry and wet AMD. Unfortunately, to date, there are no treatments to address this aspect of the disease. Treatment thus far has been limited to anti-VEGF therapy, which is highly effective in decreasing leakage from the neovascular complex; however, it is not effective in causing regression of choroidal neovascularization (CNV). This can be seen right from the start of the ophthalmic clinical experience with ranibizumab in the MARINA and ANCHOR studies. After 2 years of monthly injections of 0.5 mg of ranibizumab (Lucentis, Genentech), no regression of the CNV complexes was noted.

This leaves the door open for another treatment modality to attack a new pathway in the development of wet AMD. There is a potential role for a combination therapy approach to treatment of neovascular AMD. A key pathway in wet AMD, in addition to VEGF, is platelet-derived growth factor (PDGF). We have learned from the oncology literature that PDGF plays a role in the proliferation and maturation of new vessels. PDGF controls pericytes, cells that cover and protect most of the neovascular complex, like an armor against anti-VEGF therapy. Pericytes line the outer wall of endothelial cells and cause vascular maturation, limiting the effect of anti-VEGF therapy.

It is believed that an effective anti-PDGF agent can strip the pericytes from the neovascular complex and leave the vascular endothelial cells beneath exposed, making the anti-VEGF agent more potent again. Multiple papers in the scientific literature support this theory.

**ANTI-PDGF THERAPY**

An anti-PDGF agent is currently being developed for treatment of neovascular AMD. E10030 (Fovista, Ophthotech) is a PEGylated aptamer that binds PDGF-B, the most common form of PDGF. Animal models have demonstrated that treatment with this agent strips pericytes and leaves bare endothelial cells, which are then more susceptible to anti-VEGF therapy than to anti-VEGF therapy alone.

A phase 2b clinical trial has been conducted to assess the safety and efficacy of anti-PDGF E10030 and ranibizumab combination therapy with ranibizumab monotherapy in patients with neovascular AMD. This randomized, double-masked study is distinctive in that it was very large for a phase 2 study, enrolling 449 patients. Statistically it is notable because it was a superiority study rather than a noninferiority study.

The primary endpoint was mean change in visual acuity from baseline at the 24-week visit. Secondary endpoints included mean change in visual acuity from baseline at week 12, the proportion of subjects gaining 15 or more ETDRS letters from baseline at week 24, the proportion of subjects gaining 15 or more ETDRS letters from baseline at week 12, and mean change in area of choroidal neovascularization (defined as classic CNV plus occult CNV) on fluorescein angiography from baseline to week 24.

There were 3 arms in the study: a high dose of 10030 (1.5 mg) plus ranibizumab, a low dose of E10030 (0.3 mg) plus ranibizumab, and ranibizumab monotherapy. Treatments were administered every 4 weeks. Baseline demographics were balanced among the 3 arms.

**PHASE 2b RESULTS**

In the primary endpoint of mean change in visual acuity at 24 months, patients in the high-dose...
combination arm gained 10.6 letters, those in the low-dose combination arm gained 8.8 letters, and those in the monotherapy arm gained 6.5 letters (Figure 1; $P = .019$ for ranibizumab only in comparison with each combination group). Comparing the high-dose combination result with the monotherapy result, there was a 62% additional benefit from baseline with the addition of the anti-PDGF agent (Figure 2).

Of note, there was a continued rise in letters gained over the period of the study, and a continued separation between the vision curves in the combination and monotherapy arms. There was also a classic dose-response curve: better results with the high dose than the low dose combination, and the combination better than monotherapy at every time point (Figure 3).

A number of prespecified subgroup analyses were performed, including the effect of baseline lesion size on results. In most anti-VEGF trials in AMD, the small classic lesions seem to respond well and drive the data results. In this trial, in lesions smaller than 4 disc areas at baseline, there was more improvement in visual outcome in the high-dose combination arm than the monotherapy arm, but in eyes with larger lesions, 4 disc areas or greater, for which ranibizumab tends not to work as effectively, there was an even greater differential between visual outcome benefit with the high-dose combination and with monotherapy.

Subgroup analyses of vision gain and vision loss were also performed. Whether looking at patients who gained 3, 4, or 5 lines of vision, the combination arms were superior to the monotherapy arm. The relative benefit of combination therapy increased with the higher levels of vision gain: 27% relative benefit among 3-line gainers, 71% among 4-line gainers, and 190% among 5-line gainers.

The converse was true with vision loss: Combination therapy was protective, with fewer patients losing more
than 5 and more than 10 letters in the combination arms than in the monotherapy arm.

Regarding safety, ocular adverse events were relatively well balanced among the study arms. Intraocular pressure increase was more common in the combination arms because 2 injections were given, but these increases were transient. Systemic serious adverse events were minimal in all 3 arms.

**CONCLUSIONS**

In this large phase 2b clinical trial, a combination of E10030 anti-PDGF and ranibizumab anti-VEGF therapies met the prespecified primary endpoint of superiority ($P = .019$). A 62% additional benefit of combination therapy was seen, with classic dose-response profiles at all time points and diverging efficacy curves over time. There was a marked increase in high levels of vision gain and a diversity of data across all clinically relevant and prespecified subgroups. No additional safety concerns were seen with combination therapy.

To put the primary endpoint results in context, think of the monumental benefit ranibizumab has been to our patients with wet AMD. In this phase 2b study, ranibizumab monotherapy performed about as one would expect, with patients gaining a mean 6.5 letters of visual acuity during the first 6 months of treatment. The high-dose combination therapy resulted in a 62% additional benefit above monotherapy.

Additionally, the vision gain and vision loss subgroup analyses in this trial could have significant real-world implications. Reports from clinical trials often concentrate on 3-line gainers, but in this trial there were substantial differences in 4- and 5-line gainers as well. Perhaps we should be raising the bar regarding the kinds of benefit we aim for.

However, we should not put the cart before the horse. We now have quality phase 2 clinical trial data supporting combination therapy; we will have to wait for the phase 3 studies before drawing any firm conclusions.

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5. Benjamin LE, Hemo I, Keshet E. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. *Development.* 1998;159(9):1591-1598.