

The Rationale for Selective VEGF Inhibition

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BY THOMAS R. FRIBERG, MD

Two drugs that inhibit vascular endothelial growth factor (VEGF) have been approved by US regulators for use in the treatment of choroidal neovascularization (CNV) in age-related macular degeneration (AMD). One of these drugs, pegaptanib sodium (Macugen, OSI/Eyetech and Pfizer, both in New York, NY), selectively inhibits the most biologically active isoform of VEGF, VEGF₁₆₅.¹ The other drug, ranibizumab (Lucentis, Genentech, San Francisco), nonselectively targets all known isoforms of VEGF-A.^{2,3} Another VEGF-blocking drug, bevacizumab (Avastin, Genentech), has also recently been used for treatment of CNV in AMD, although it was not developed for ocular use and has not been approved for that indication.

Although VEGF inhibition is the goal of all these drugs as well as several other compounds in development for the treatment and prevention of CNV, it should not be forgotten that VEGF is an important compound for the normal function of the human body. VEGF is essential during fetal development⁴ and in the female reproductive cycle,⁵ and it has been shown to be expressed in nonangiogenic tissues in the brain, the kidney and the gastrointestinal (GI) mucosa.⁵

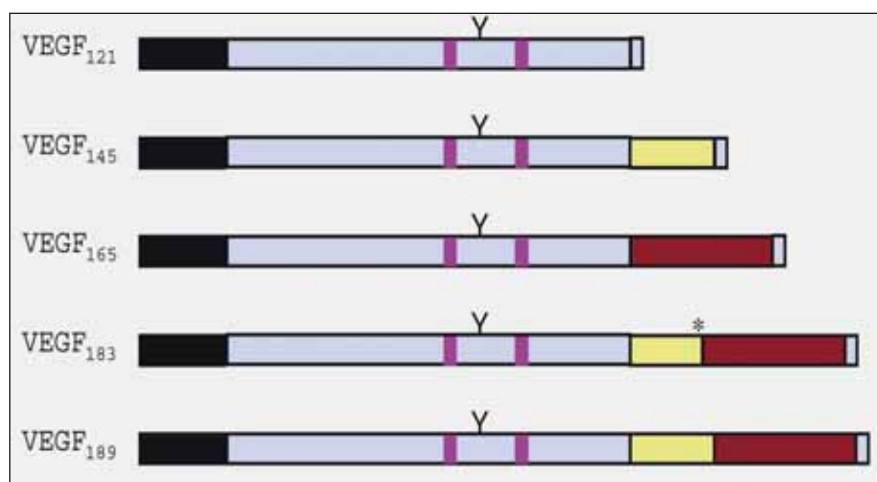


Figure 1. VEGF-A isoforms conserved through evolution.

VEGF has also been shown to be necessary for the maintenance of capillaries⁶ and for the normal development of ocular tissues such as the choriocapillaris.⁷

Several epidemiologic studies have shown an increased risk of cardiovascular disease, hypertension, and cardiovascular events including stroke and myocardial infarction, in people with AMD.⁸⁻¹⁰ Given that systemic nonselective VEGF inhibition may be associated with an increased risk of thromboembolic events,¹¹ and that repeated intravitreal delivery of VEGF inhibitors inevitably involves systemic exposure to these VEGF-blocking agents,⁵ it is important to consider the systemic safety of these ocular treatments in the AMD patient population, especially over the long term.

SAFETY REVIEW

Pegaptanib has an excellent safety profile in clinical trials for up to 3 years. In the two VEGF Inhibition Study in Ocular Neovascularization (VISION) trials,^{12,13} the safety of pegaptanib was assessed in all patients who received at least one treatment. Those studies found no apparent systemic or ocular safety issues. Cardiovascular events and all-cause mortality were comparable in the groups receiving pegaptanib and sham injections. There was also no clinical or angiographic evidence of damage to the retina or choroid after 3 years of intravitreal injections of pegaptanib.

Bevacizumab and ranibizumab, although they were developed from the same murine monoclonal antibody source,¹⁴⁻¹⁷ are distinct molecules that were developed for different diseases (cancer and AMD, respectively) using differing strategies and methods. Their safety implications should therefore be discussed separately.

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In the Minimally Classic/Occult Trial of the Anti-VEGF Antibody RhuFab V2 in the Treatment of Neovascular AMD (MARINA) study,¹⁸ 716 patients with minimally classic or occult AMD were randomly assigned in equal numbers to receive sham injection or one of two doses of ranibizumab, 0.3 mg or 0.5 mg, once a month for 2 years. The rates of arterial thromboembolic events among the three groups were not statistically significantly different. It is notable, however, that at 1 year in this study there were no deaths in the sham injection group, one death (0.4%) in the 0.3-mg group due to MI, and two deaths (0.9%) in the 0.5-mg group, one due to small bowel infarct and one due to chronic obstructive pulmonary disease.

The Food and Drug Administration (FDA)-approved labeling of ranibizumab cautions that there is a theoretical risk of thromboembolic events after intravitreal injection of a VEGF inhibitor.¹⁹ The labeling notes that, in the data from three clinical trials submitted to the FDA for approval of the drug, the rate of arterial thromboembolic events in the first year was 2.1% in the 874 patients who received either the 0.3-mg or 0.5-mg doses of ranibizumab, versus 1.1% in the 441 control patients. In the second year of one of those trials, however, the rate of thromboembolic events in the treated and sham groups was similar (3.0% and 3.2% respectively).

Genentech issued a letter to physician-users (a so-called "Dear Doctor" letter) in January noting safety concerns in an interim safety analysis in the ongoing Safety assessment of intravitreal Lucentis for AMD (SAILOR) trial.²⁰ Analysis showed a higher incidence of strokes in the group receiving the 0.5-mg (1.2%) than in the group receiving the 0.3-mg dose (0.3%) at an average follow-up of 230 days. Patients with previous history of stroke appeared to be at higher risk for stroke during the trial. No difference between groups was seen for MI or vascular death. The 1-year data from the SAILOR trial are pending.

Bevacizumab is approved by the FDA for systemic use in the treatment of colorectal cancer. The labeling for bevacizumab²¹ includes a "black box" warning regarding risk of GI perforation and arterial thromboembolic events with IV infusion at a dose of 5 mg/kg. The manufacturer, Genentech, discontinued a clinical trial in 2005 for treatment of refractory ovarian cancer because five of 44 patients developed GI perforations.

SYSTEMIC LEVELS

Animal studies have suggested that an intravitreal injection of VEGF inhibitors may be sufficient to cause VEGF inhibition systemically. Plasma levels of 0.4 µg/mL have been detected after bilateral injections of 0.5 mg pegaptanib in rhesus monkeys.²² Plasma levels of 150 ng/mL have been seen after bilateral injection of 0.5 mg ranibizumab in cynomolgus monkeys.²³ In contrast, plasma VEGF levels in the normal human adult are usually less than 100 pg/mL, two orders of magnitude lower than the observed levels in monkeys after intravitreal injection.²⁴ The effects of chronic low-level VEGF blockade are not known.

The plasma half-life of bevacizumab after a 1.25-mg intravitreal injection in humans is 14 to 28 days.²⁵ It has been suggested that a contralateral effect can be seen in the untreated fellow eye after intravitreal administration of bevacizumab.²⁶

TREATMENT STRATEGY

AMD is a chronic disease, and all of the VEGF-inhibiting drugs currently available rely on repeated doses, potentially for the rest of our patients' lives. Given the excellent ocular and systemic safety profile of the selective VEGF inhibitor pegaptanib and the theoretical systemic safety risks with the nonselective VEGF inhibitors, it makes sense to try to design a treatment strategy that will minimize patients' exposure to systemic cardiovascular risks.

Clinical data suggest that nonselective VEGF inhibition can improve vision in a significant percentage of patients, and that this improvement may stabilize after a few injections. A trial has been designed to evaluate whether these

gains can be maintained with selective VEGF inhibition.

The ongoing Open-label, Phase 4 Evaluation of Efficacy and Safety in Maintaining Visual Acuity with Sequential Treatment of Neovascular AMD (LEVEL) trial is assessing an induction-maintenance strategy of VEGF inhibition. Before entry in the trial, visual improvement and anatomic response are first induced by the use of one to three treatments for wet AMD, and then the subject is placed in the LEVEL trial to determine if these effects can be maintained with pegaptanib sodium given every 6 weeks. The vast majority of subjects to date have been induced with non-selective VEGF blockade, but other treatments are also allowed for induction. "Booster" treatment with additional therapy may be given if the investigator believes that the disease has progressed according to guidelines. Efficacy endpoints include the percentage of patients who maintain baseline vision or improve at the 54-week follow-up point as well as mean change in visual acuity over time.

The ongoing open-label, phase 4 LEVEL trial is assessing an induction-maintenance strategy of VEGF inhibition.

A planned interim analysis of the LEVEL trial including the first patients completing 18 and 24 weeks of maintenance with pegaptanib was recently presented.²⁷ Most subjects were "dry" (with retinal thickness of 200 µm or less) at the end of the induction phase and experienced visual improvement during induction. Subjects have demonstrated visual and anatomic stability during the maintenance phase with a safety profile similar to those in the VISION trials.

It appears that maintenance with pegaptanib in this trial reduces patients' exposure to nonselective anti-VEGF agents while retaining the visual gains seen during induction. This may be of particular importance for our patients at high risk of cardiovascular events. ■

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