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Clinical Evaluation of Pazopanib Eye Drops versus Ranibizumab Intravitreal Injections in Subjects with Neovascular Age-Related Macular Degeneration

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Purpose: To evaluate pazopanib eye drops in subjects with active subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Design: Multicountry, randomized, parallel-group, double-masked, active and placebo-controlled, dose-ranging study of eye drops.

Participants: A total of 510 subjects (93% white; 58% female; mean age, 75.3 years) whose AMD was previously managed by anti–vascular endothelial growth factor intravitreal injections.

Methods: Treatments administered for 52 weeks included placebo eye drops instilled 4 times daily (n = 73); pazopanib 5 mg/ml instilled 3 (n = 72) or 4 times daily (n = 74); pazopanib 10 mg/ml instilled 2 (n = 73), 3 (n = 73), or 4 times daily (n = 72); or ranibizumab injection administered once every 4 weeks (n = 73). In addition, for all eye drop treatment groups, open-label ranibizumab was administered as needed.

Main Outcome Measures: The main outcome measures were best-corrected visual acuity (BCVA) and injection frequency assessed at week 52. Safety was assessed every 4 weeks and pazopanib plasma concentrations were determined at weeks 4 and 24.

Results: At week 52, pazopanib, with allowance for as-needed ranibizumab injections, was noninferior to monthly ranibizumab as well as to as-needed ranibizumab administered with placebo eye drops in maintaining BCVA (estimated BCVA gains of 0.3–1.8 vs. 1.4 vs. 0.2 letters, respectively). Pazopanib treatment did not reduce as-needed ranibizumab injections by ≥50% (prespecified efficacy criterion). At week 52, there were no clinically meaningful changes from baseline in retinal thickness or morphology, CNV size, or lesion characteristics on optical coherence tomography or fluorescein angiography. Complement factor H genotype had no effect on the responses to pazopanib and/or ranibizumab (BCVA, injection rate, or optical coherence tomography/fluorescein angiography changes). Steady-state concentrations of pazopanib in plasma seemed to be reached by week 4. The most common ocular adverse events related to pazopanib and ranibizumab were application site pain (3%) and injection site hemorrhage (1%), respectively. No treatment-related serious adverse events were reported.

Conclusions: Pazopanib was well tolerated. Daily pazopanib eye drops in neovascular AMD subjects did not result in therapeutic benefit beyond that obtained with ranibizumab alone. *Ophthalmology 2015;122:579-588 © 2015 by the American Academy of Ophthalmology.*

Supplementary material is available at www.aaojournal.org.

Angiogenesis is a key factor in the progression of age-related macular degeneration (AMD).[1] In the late stage of AMD, choroidal neovascularization (CNV) may cause leakage of blood or serum and macular scarring leading to vision loss.[2,3] Angiogenesis pathways are, therefore, important targets for pharmacologic therapies of neovascular AMD.

The vascular endothelial growth factor (VEGF) pathway is a clinically validated target in the treatment of neovascular AMD. Ranibizumab (a humanized monoclonal VEGF antibody fragment), bevacizumab (a recombinant monoclonal VEGF antibody), and aflibercept (a fusion protein) bind with high affinity to and neutralize all biologically active isoforms of VEGF.[4,5] Therapy with these agents is common and highly effective for the treatment of neovascular AMD.[6,7]

At the time that this clinical study was initiated, ranibizumab was the only licensed agent for the treatment of AMD, with a labeled treatment regimen of once-monthly injections. Although highly effective and representing a

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major advance over previous therapies, not all patients who were treated with ranibizumab recovered full visual function.[8] Furthermore, monthly treatments, which are required to be delivered by direct injection into the vitreous,[9] are considered burdensome for patients.[10] As a result, there existed a potential benefit for availability of a noninvasive intervention that maintained or improved visual acuity (VA) while reducing the number of intravitreal (IVT) injections.

Pazopanib is a multitarget tyrosine kinase inhibitor that inhibits VEGF receptors (1, 2, and 3) as well as the proangiogenic platelet-derived growth factor pathway.[11] In animal models, twice-daily oral, periocular, or topical dosing with pazopanib prevented the progression of laser-induced CNV.[12,13] A topical ocular formulation of pazopanib, a self-administered therapy, was investigated for the treatment of neovascular AMD. An earlier proof-of-concept phase II clinical study showed that the topical ocular instillation of pazopanib 5 mg/ml eye drops 3 times daily (TID) was associated with improved best-corrected VA (BCVA) in subjects with subfoveal CNV secondary to AMD.[14] A post hoc pharmacogenetic analysis suggested that BCVA and optical coherence tomography (OCT) effects were strongest in the subjects carrying the TT genotype of the *complement factor H* (*CFH*) Y402H polymorphism.[14]

This article describes the results of a dose-ranging clinical study that evaluated whether daily dosed pazopanib eye drops could maintain or possibly improve vision while reducing the continued need for IVT injections in subjects with previously treated neovascular AMD and active subfoveal CNV in the study eye. In addition, this study evaluated the safety, tolerability, and retinal changes associated with the use of topical ocular pazopanib and determined the steady-state plasma pazopanib concentrations after topical ocular administration.

Methods

Study Design

This was a phase IIb, multicountry, multicenter, randomized, parallel-group, double-masked (eye drops), active and placebo-controlled, dose-ranging study. Eligible subjects were randomized according to a computer-generated randomization list (1:1:1:1:1:1:1:1) using an interactive voice response system to 1 of 7 treatment groups for a 52-week treatment period: pazopanib 5 mg/ml eye drops TID; pazopanib 5 mg/ml eye drops 4 times daily (QID); pazopanib 10 mg/ml eye drops 2 times daily; pazopanib 10 mg/ml eye drops TID; pazopanib 10 mg/ml eye drops QID; placebo eye drops; or open-label ranibizumab IVT injection once every 4 weeks.

Pazopanib and placebo eye drops were instilled as 1 drop in the study eye (only 1 eye per subject) according to the dosing regimen. The pazopanib eye drops were double masked with placebo eye drops as applicable, such that all subjects instilled study drug on a QID regimen. Thus, if the masked dosing regimen for the active study drug was less than QID, the subject instilled placebo eye drops in the remaining dosing intervals (e.g., a 2 times daily dose of active drug equated to dosing of pazopanib eye drops at 2 time points during the day [morning and dinner] plus dosing of placebo eye drops at 2 additional time points during the day [midday and bedtime] to achieve an overall QID study drug dosing regimen). Each eye drop container was overwrapped using aluminum foil. The investigator or treating physician may have unmasked a subject's eye drop treatment assignment only in the case of an emergency, when knowledge of the eye drop study treatment was essential for the appropriate clinical management or welfare of the subject. Note that, to avoid a delay in treatment, and to standardize all subjects at the start of the study drug dosing period, subjects received an IVT injection of open-label ranibizumab at the end of the screening visit, approximately 1 to 2 weeks before randomization.

From weeks 4 through 52, inclusive, open-label ranibizumab IVT injection was administered as needed to subjects in the placebo group and all pazopanib groups if, in the opinion of the investigator, reinjection criteria were met (i.e., the maximum number of as-needed injections on study was 13). The protocol-defined reinjection criteria, monitored at all treatment visits after baseline, were based on monthly VA and ocular imaging evaluations and results of previous clinical studies.[15,16] Specifically, the investigator interpreted each OCT scan, BCVA score, and available fundus photography/fluorescein angiography (FA) data from weeks 4 through 52, inclusive, and were allowed reinjection per protocol if one or more of the following criteria were met: (1) evidence of intraretinal (IR) fluid (with or without cysts) or subretinal (SR) fluid, including subfoveal and/or extrafoveal accumulations, but not serous retinal pigment epithelium detachments; (2) a serous retinal pigment epithelial detachment (PED) that the investigator judged to benefit from reinjection; (3) a notable decline in VA (defined as a decrease of >5 letters from any earlier maximum acuity value measured during the study) if, in the opinion of the investigator, the decline was due to neovascular AMD); (4) a new SR or IR macular hemorrhage that the investigator judged to be associated with CNV; (5) increased lesion size on FA relative to the last angiogram as judged by the investigator; or (6) leakage on FA that the investigator judged likely to benefit from reinjection. The investigator could choose to suspend reinjection if any of these abnormalities persisted without improvement after 3 consecutive monthly reinjections.

Efficacy, reinjection criteria, and safety were assessed every 4 weeks over the 52-week study period. Additionally, a blood sample was collected for pharmacogenetic analysis. A total of 30 genetic variants in the following 17 genes were genotyped (Table 1, available at www.aaojournal.org): *CFH*, complement factor B, interleukin 8, *VEGF*, *CF1*, complement component 2, complement component 3, complement component 5, fibroblast growth factor receptor 2, age-related maculopathy susceptibility 2, serine peptidase 1, hypoxia-inducible factor 1-alpha, human hepatic lipase, cholesteryl ester transfer protein, pigment epithelium-derived factor, apolipoprotein E, and synapsin 3/tissue inhibitor of metalloproteinase 3. All subjects who were randomized to placebo eye drops or pazopanib eye drops had a single blood sample drawn for assessment of pazopanib plasma concentrations at the week 4 and 24/early withdrawal visits (if the early withdrawal visit was before week 24).

Subjects

This study included male subjects and female subjects with no childbearing potential. All subjects were required to be ≥50 years old. Eligible subjects had AMD with an active subfoveal CNV lesion secondary to AMD previously managed with, and responsive to, anti-VEGF IVT injection therapy. At the time of the screening visit, the enrolled subjects were in need of reinjection based on OCT evidence of SR fluid, central IR fluid, and/or IR cysts. Other criteria included a total lesion ≤12 disc areas, with CNV contributing ≥50% of the total lesion area. If non-CNV lesion components were present, then the following limitations must have been met: serous retinal PED; fibrosis; an atrophic scar and SR hemorrhage that, combined, were <50% of the total lesion