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Emerging therapies for the treatment of wet age-related macular degeneration – VEGF Trap-Eye

Najnowsze metody leczenia wysiękowej postaci zwyrodnienia plamki związanego z wiekiem (AMD) – VEGF Trap-Eye

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Summary: Age-related macular degeneration (AMD) is the leading cause of blindness in the industrialized world. The most severe form of this disease is exudative AMD. It accounts for 10% of cases of AMD and is responsible for approximately 90% cases of severe vision loss due to AMD. Anti-vascular endothelial growth factor (VEGF) therapy changed the standard-of-care for this blinding disease. This article presents one promising new drug for the treatment of exudative AMD – VEGF Trap-Eye.

Key words: wet age-related macular degeneration, vascular endothelial growth factor, VEGF Trap-Eye, choroidal neovascularization.

Streszczenie: Zwyrodnienie plamki związane z wiekiem (AMD) jest wiodącą przyczyną upośledzenia widzenia u mieszkańców krajów dobrze rozwiniętych. Najcięższą formą choroby jest jej wysiękowa postać. Stanowi ona około 10% wszystkich przypadków i odpowiada za 90% przypadków utraty widzenia w przebiegu AMD. Terapia wykorzystująca inhibitory naczyniowego śródbłonkowego czynnika wzrostu (VEGF) zmieniła standardy leczenia wysiękowej postaci AMD. Niniejszy artykuł przedstawia nowy, obiecujący lek, którym jest VEGF Trap-Eye.

Słowa kluczowe: wysiękowa postać zwyrodnienia plamki związanego z wiekiem, naczyniowy śródbłonkowy czynnik wzrostu, VEGF Trap-Eye, neowaskularyzacja.

Exudative AMD is complicated by choroidal neovascularization (CNV). The pathogenesis of this process is not completely understood. It is a well-established fact that one of the stimulatory factors involved is vascular endothelial growth factor (VEGF). VEGF binds to its receptors – VEGFR1 and VEGFR2, and activates kinase cascades. Signaling through this pathway promotes proliferation of endothelial cells and increase vascular permeability. An increased level of VEGF was observed in experimental model of CNV (1,2) and patients with wet AMD (3). VEGF binding agents revolutionized the treatment of exudative AMD. Ranibizumab (approved by the FDA in 2006), have been shown to provide very good visual outcomes and anatomic correction. However it has to be administered monthly to achieve desirable effect. An extensive effort has been made to explore alternative treatment options that would decrease the frequency of patient visits and injections. VEGF Trap-Eye (aflibercept ophthalmic solution), is a promising new drug for exudative AMD treatment.

VEGF Trap-Eye is a recombinant protein consisting of the binding proteins of VEGF receptors (VEGFR1 and VEGFR2) and Fc region of human antibody IgG. VRGF Trap-Eye binds all VEGF isoforms and placenta growth factor. It has high affinity and binds VEGF more tightly than other available VEGF binding agents (about 140 times that of ranibizumab). The binding activity of 2 mg VEGF Trap-Eye at 83 days estimated to be comparable to the activity of 0.5 mg ranibizumab at 30 days (4). The potential benefit of VEGF Trap-Eye is a sustained effect compared to other anty-VEGF agents.

The phase I clinical trial assessing the therapeutic effect of aflibercept was called Clinical Evaluation of Angiogenesis in the Retina (CLEAR). It was a randomized, double-masked, ascending dose, placebo-controlled study of 18 patients with neovascular AMD who received either placebo or single doses of VEGF Trap (0.3 mg/kg, 1.0 mg/kg or 3.0 mg/kg). Nguyen et al. (5) found a dose-dependent decrease in the central retina thickness. Because of a side effect – dose-dependent increase in blood pressure, further studies of systemic VEGF Trap were halted. In the CLEAR IT-1 study (phase I) a single intravitreal injection of multiple doses of VEGF Trap-Eye was used (0.05 mg,

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0.15 mg, 1 mg, 2 mg, and 4 mg), and after 6 weeks resulted in statistically significant gains in visual acuity and central retinal thickness reduction (6,7).

The phase II trial (CLEAR IT-2) demonstrated that VEGF Trap-Eye is safe, well tolerated and highly effective in exudative AMD treatment. In this double-masked, prospective, randomized, multi-center study, 157 patients with AMD were treated with VEGF Trap-Eye in one eye during 52 weeks. Patients were divided into five groups and were initially treated with either fixed monthly (0.5 mg, 2 mg) or quarterly (0.5 mg, 2.0 mg, 5.0 mg) doses for 12 weeks, and then continued to receive therapy at the same dose on the PRN (as needed) dosing schedule. Patients were monitored for safety, retina thickness measured by OCT (Optical Coherent Tomography), and visual acuity. The best result was achieved in the group of patients receiving four monthly doses of 2.0 mg VEGF Trap-Eye for 12 weeks and during the PRN dosing period, on average, only 1.6 additional injections. These patients exhibited a mean improvement in visual acuity of 9.0 letters and mean decrease in retinal thickness of 143 μm at week 52 versus baseline. For all dose cohorts combined, there was a 5.3 mean letter gain in visual acuity and 130 μm mean decrease in retinal thickness. Patients from all dose groups received, on average, only two additional injections of VEGF Trap-Eye over 40 weeks after 12 weeks fixed dosing period (8-10).

The VIEW (VEGF Trap-Eye Investigation of Efficacy and Safety in Wet AMD) program is a global, randomized, double-masked, phase III clinical trial evaluating VEGF Trap-Eye in the treatment of the neovascular form of AMD, in comparison to the current standard of care ranibizumab (Lucentis). The VIEW program consist of two studies: the VIEW 1 study which is being conducted in the United States and Canada by Regeneron and the VIEW 2 study which is being led in Europe, Asia Pacific, Japan and Latin America by Bayer HealthCare. The studies gathered 2457 patients, who were divided into groups and received intravitreal injections of VEGF Trap-Eye on a schedule of 0.5 mg every 4 weeks, 2 mg every 4 weeks, 2 mg every 8 weeks or 0.5 mg of ranibizumab every 4 weeks during the first year of the study. In the second year of each study PRN dosing will be evaluated. Data over 52 weeks of the study indicates that all 3 VEGF Trap-Eye dose regiments, and, in particular, 2 mg VEGF Trap-Eye dosed every 8 weeks, provided similar therapeutic effects as ranibizumab. In the VIEW 1 study 96% of patients receiving VEGF 0.5 mg monthly, 95% of patients receiving VEGF 2.0 mg monthly, and 95% of patients receiving VEGF 2.0 mg every two months achieved maintenance of vision compared to 94% of patients receiving ranibizumab 0.5 mg dosed every month. In the international VIEW 2 study the comparisons were similar. Additionally, in the VIEW 1 study, patients receiving 2 mg of VEGF Trap-Eye monthly achieved a statistically significant greater mean improvement in visual acuity (10.9 letters), compared to patients who received ranibizumab 0.5 mg every month (8.1 letters). Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye charts, and maintenance of vision was defined as losing fewer than three lines (equivalent to 15 letters). VEGF Trap-Eye was generally well tolerated. The most common ocular adverse events not related to the underlying disease, were those associated with the intravitreal injection procedure, e.g. conjunctival hemorrhage, retinal hemorrhage, vitreous detachment, vitreous floaters and eye pain. Serious ocular adverse reactions have occurred very rare (<0,1% of intravitreal injections) and included endophthalmitis, traumatic cataract, and transient increased IOP. The most frequent serious non-ocular side effects were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD (11,12).

After these positive results, Beyer HealthCare and Regeneron are planning to submit regulatory application for marketing approval of VEGF Trap-Eye for wet AMD in Europe and the US. The recommended VEGF Trap-Eye therapy begins with one injection per month for three consecutive months, followed by one injection every two months. This dosing regimen provide efficient therapy for exudative AMD with a decreased risk for adverse injection-related events. Simultaneously clinical trials are being conducted to evaluate VEGF Trap-Eye in the treatment of Central Retinal Vain Occlusion [GALILEO (13), COPERNICUS (14)] and Diabetic Macular Edema [DA VINCI (15)]. Results from all of these trials are promising and demonstrate the wide-range of applications for VEGF Trap-Eye in ophthalmology (16).

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