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Current use of aflibercept 8 mg (Eylea HD) in retinal diseases

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ABSTRACT

Aflibercept 8 mg (Eylea HD) has emerged as a pivotal agent in the treatment of retinal diseases and has begun to showcase its efficacy and innovation in the field of ophthalmology. This article delves into the current use of aflibercept 8 mg, exploring its applications, mechanisms of action, and impact on the treatment landscape for various retinal conditions. This review provides an overview of recent clinical studies and highlights the key findings and advancements associated with the use of 8 mg aflibercept.

Keywords: Aflibercept 2 mg, aflibercept 8 mg, eylea HD, ophthalmology, retina, vascular endothelial growth factor

INTRODUCTION

The relentless pursuit of advances in medical science continues to bring groundbreaking innovations. Among these, aflibercept 8 mg (Eylea HD; Regeneron Inc., Tarrytown, NY) holds the hope of reshaping the landscape of retinal disease management. Aflibercept 8 mg is one of the results of the search for effective and targeted interventions in retinal diseases, representing a paradigm shift.[1]

This article explores the multifaceted facets of aflibercept 8 mg, investigating its current applications, mechanisms of action, and dynamic impact on the treatment landscape. Through an in-depth examination of recent clinical studies and emerging trends, we aimed to unravel the potential challenges associated with the utilization of aflibercept 8 mg in diverse retinal diseases.

MECHANISM OF AFLIBERCEPT 8 MG

Aflibercept 2 mg (Eylea; Regeneron Inc., Tarrytown, NY, USA) is commonly used to treat certain eye conditions, particularly neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), diabetic retinopathy (DR), macular edema following retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), and retinopathy of prematurity (ROP). The drug works by targeting vascular endothelial growth factor (VEGF), a protein that plays a crucial role in the formation of abnormal blood vessels in the eye.[2]

Aflibercept acts as a VEGF-A and placental growth factor (PlGF) inhibitor. By binding to these proteins, aflibercept inhibits their ability to stimulate the growth of abnormal blood vessels in the retina.2 Aflibercept is a fusion protein of VEGFR-1 (second portion) and VEGFR-2 (third portion), and the Fc portion of human immunoglobulin G (Ig-G). It contains entirely human amino acid sequences and binds to VEGF-A and PlGF. The second Ig fragment of VEGFR-1 was chosen because it showed high binding properties with VEGF. PlGF binds to VEGFR-1, facilitating VEGF-A activity primarily through VEGFR-2. In addition to aflibercept directly binding and inhibiting VEGF-A, it also has the effect of binding to PlGF and reducing the effect of VEGF-A.[3]

While aflibercept 2 mg is effective in the treatment of nAMD, DME, DR, RVO, mCNV and ROP, it has not completely solved the problem of frequent admission to outpatient clinics due to its short duration of action, and the search for a longer-acting drug has emerged.[3]

The "HD" in aflibercept 8 mg (Eylea HD) indicates a higher dose. The maximum feasible dose, constrained by solubility considerations, was 8 mg, administered in 70 µL. This represents a slightly larger volume than that of the typical anti-VEGF injection (50 µL). Aflibercept 8 mg has been approved for the treatment of various eye conditions, including nAMD, DME, and DR. Its mechanism of action revolves around targeting specific proteins called VEGF and PlGF.[4]

By inhibiting VEGF activity, aflibercept 8 mg can reduce fluid buildup in the macula, stabilizing and potentially improving vision, preventing further vision loss, and increasing the interval between treatment injections. Additional important points about the mechanism of aflibercept 8 mg are as follows. a)Broader targeting: Compared to some other anti-VEGF medications, aflibercept binds to a wider range of VEGF molecules (VEGF-A, VEGF-

B, and PlGF), offering potentially more comprehensive inhibition. b) Longer-lasting effect: Aflibercept 8 mg allows for longer-lasting VEGF inhibition and potentially less frequent injections compared to other medications.[4]

CLINICAL STUDIES WITH AFLIBERCEPT 8 MG IN AGE-RELATED MACULAR DEGENERATION

Aflibercept (8 mg) was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The FDA approved an aflibercept injection 8 mg for the treatment of nAMD, DME, and DR in August 2023. The EMA has recommended the approval of 8 mg aflibercept for the treatment of nAMD, DME, and DR in November 2023. In addition, the European Commission granted marketing authorization for 8 mg of aflibercept in January 2024. Here, we summarize key clinical studies investigating the use of 8 mg aflibercept in AMD.

1. CANDELA Trial

This was a randomized, single-blinded, multicenter study involving 106 eyes with nAMD. Patients were randomly assigned to receive 3 monthly doses of aflibercept (8 mg, 70 µL) or aflibercept (2 mg, 50 µL), followed by doses at weeks 20 and 32. The main outcome measures were the percentage of eyes lacking fluid (defined as the absence of intraretinal and subretinal fluid) in the central subfield on spectral-domain optical coherence tomography (SD-OCT) at week 16 and safety, evaluated by the occurrence of ocular treatment-emergent adverse events (TEAEs) and serious TEAEs up to weeks 4 and 44. Additional exploratory endpoints included the percentage of eyes without fluid in the central subfield at week 44 and in the macula at weeks 16 and 44; the percentage of participants experiencing vision loss or gain at week 44; and changes from baseline in central retinal thickness, total lesion size, choroidal neovascularization size, and best-corrected visual acuity (BCVA) score at week 44. In the study results, it was observed that at week 16, 50.9% of eyes in the 8-mg group showed no fluid, whereas only 34.0% in the 2-mg group exhibited the same. By week 44, the percentage of eyes without fluid was 39.6% in the 8-mg group compared to 28.3% in the 2-mg group, accompanied by a mean change in BCVA of +7.9 vs. +5.1 letters, respectively. Notably, no discernible safety differences were noted between the two groups. It is important to note that CANDELA was primarily a safety study, and the results suggest that 8 mg of aflibercept is well tolerated with extended dosing intervals. However, further research is necessary to definitively compare its efficacy against the standard aflibercept regimen.[5]

2. PULSAR Trial

This Phase 3, double-blinded, randomized study compared aflibercept 8 mg and aflibercept 2 mg in 1009 patients with nAMD. Participants received either: a) aflibercept 2 mg every 8 weeks after three initial monthly injections b) Aflibercept 8 mg every 12 weeks after three initial aflibercept injections c) Aflibercept 8 mg every 16 weeks after the three initial monthly injections. The primary endpoint analysis of PULSAR at 48 weeks demonstrated the non-inferiority of the 8-mg dose compared to the 2-mg dose. The results at 60 and 96 weeks indicated that 91.5% of all patients in the PULSAR completed the 60-week assessment, with an average discontinuation rate of 7.9% before 60 weeks. In terms of BCVA, all three treatment arms exhibited similar improvements and maintenance at 48, 60, and 96 weeks. The gains, measured in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, were 7, 6.1, and 5.9 in the aflibercept 2 mg every 8 weeks, aflibercept 8 mg every 12 weeks, and aflibercept 8 mg every 16 weeks arms at 48 weeks; 7.2, 6.4, and 6.3 letters at 60 weeks; and 6.6, 5.6, and 5.5 letters at 96 weeks. The reduction in the central retinal subfield thickness (CST), measured using SD-OCT, followed a similar pattern. The reductions were 136 µm in the aflibercept 2 mg every 8 weeks arm and 147 µm in the aflibercept 8 mg every 12 weeks and aflibercept 8 mg every 16 weeks arm at 48 weeks; 155, 154, and 151 µm arm at 60 weeks; and 147, 152, and 149 µm arm at 96 weeks. Aflibercept 8 mg demonstrated a similar safety profile to aflibercept 2 mg.[6]

CLINICAL STUDIES WITH AFLIBERCEPT 8 MG IN DIABETIC MACULAR EDEMA AND DIABETIC RETINOPATHY

Several clinical studies have investigated its efficacy and safety under these conditions, providing valuable insights for healthcare professionals and patients. A summary of the key trials is as follows:

PHOTON Trial

This Phase 3, double-masked, randomized study compared 8 mg aflibercept with 2 mg aflibercept in patients with DME. Participants received: a) aflibercept 2 mg every 8 weeks after five initial monthly injections b) Aflibercept 8 mg every 12 weeks after three initial monthly injections c) Aflibercept 8 mg every 16 weeks after the three initial monthly injections. The PHOTON trial successfully achieved its primary endpoint, demonstrating that patients receiving aflibercept 8 mg attained vision gains equivalent to aflibercept 2 mg, with approximately 90% maintaining 12- and 16-week dosing regimens during the first year. The mean number of injections administered were 9.5 for the 12-week aflibercept 8 mg group, 7.8 for the 16-week aflibercept 8 mg group, and 13.8 for the aflibercept 2 mg groups. A significant majority of aflibercept 8 mg patients sustained extended dosing intervals.[7]

The key findings from the study are as follows:

- 89% of patients maintained ≥12-week dosing intervals, compared to 93% in one year.
- 84% maintained ≥16-week dosing intervals, compared to 89% maintaining a 16-week dosing interval through one year, among those randomized to a 16-week dosing interval at baseline.
- At week 96, 44% met the criteria for ≥20-week dosing intervals, including 17% and 27% eligible for 20- and 24-week dosing intervals, respectively.
- The safety profile of aflibercept 8 mg remained similar to that of aflibercept 2 mg over two years and aligned with the known safety profile of aflibercept 2 mg from prior clinical trials for DME.
- TEAEs, including cataracts, vitreous floaters, and conjunctival hemorrhage, occurred in 5% of patients in any treatment group.
- No cases of retinal vasculitis, occlusive retinitis, or endophthalmitis have been reported. The rate of intraocular inflammation was 1.2% in both the aflibercept 2 mg and aflibercept 8 mg groups.

- Arterial thromboembolic TEAEs, as defined by the Anti-platelet Trialists' Collaboration, occurred in 7.2% of patients treated with aflibercept 2 mg and 6.7% of patients treated with aflibercept 8 mg.[7]

CLINICAL STUDIES WITH AFLIBERCEPT 8 MG IN MACULAR EDEMA WITH BRANCH AND CENTRAL RETINAL VASCULAR OCCLUSION

Aflibercept 8 mg has not been approved for the treatment of macular edema (ME) with branch or central retinal vein occlusion (BRVO and CRVO). Although it shows promise and is being investigated in this area, further research is needed before it becomes a standard treatment option. Although Aflibercept 8 mg has not received official approval for BRVO/CRVO, ongoing clinical studies are assessing its efficacy and safety. A promising study includes the following.

QUASAR Phase 3 Trial

While primarily focused on ME secondary to CRVO, the QUASAR study also included a small subgroup of patients with ME secondary to BRVO. This trial evaluates the efficacy and safety of 8 mg aflibercept compared to standard aflibercept 2 mg, with BCVA change at year 1 as the primary endpoint. Early data may emerge by late 2024, offering further insights into the potential of 8 mg aflibercept in both BRVO and CRVO-related ME.

The QUASAR trial is a global, randomized, double-masked, active-controlled phase III study designed to assess the efficacy and safety of aflibercept 8 mg when used with extended dosing regimens in cases of macular edema secondary to retinal vein occlusion. The primary endpoint of the study was to record the change in BCVA, measured using the ETDRS letter score, from the date of randomization through 36 weeks of treatment. In this trial, BCVA changes were compared between two groups of patients: those who received aflibercept 8 mg with extended treatment intervals following initial monthly doses and those who received aflibercept 2 mg every 4 weeks. The treatment intervals may be further adjusted based on the response to treatment. Patients will be treated for up to week 60, followed by a monitoring period extending to week 64. The trial aims to enroll approximately 800 patients.[8]

CONCLUSION

Aflibercept 8 mg may represent a significant advancement in the treatment of retinal diseases. Its high-dose formulation may offer the potential for extended treatment intervals, potentially reducing patient burden and promoting treatment adherence. While currently approved for nAMD, DME, DR, ongoing research explores its efficacy in other conditions like RVO, mCNV and ROP.[9]

Randomized clinical trials have demonstrated the effectiveness of 8 mg aflibercept in improving vision and stabilizing disease progression across the approved indications. Its safety profile seems comparable to that of the standard aflibercept 2 mg version, although further long-term data are needed. Although not devoid of potential challenges, including higher cost and the need for further research in certain areas, aflibercept 8 mg shows promise in the management of retinal diseases.

Continued clinical investigations will refine our understanding of the role of 8 mg aflibercept in treating additional retinal conditions. Optimizing treatment regimens, potentially reducing the injection frequency further, and ensuring wider accessibility remain key priorities.

ETHICAL DECLARATIONS

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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