Review Article

Approved pharmacotherapy for myopic choroidal neovascularization: a review of randomized controlled trials in ranibizumab and aflibercept

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Abstract: Myopic choroidal neovascularization (mCNV) can cause severe visual impairment in highly myopic patients. We review the randomized trials of two approved pharmacotherapy for treating mCNV, including intravitreal injections of ranibizumab and aflibercept. These two vascular endothelial growth factor (VEGF) antagonists show superior ability to improve vision and reduce macular thickness, comparing with sham injections or verteporfin photodynamic therapy (vPDT). There is no severe ocular or systemic adverse reaction reported in studies associated with ranibizumab and aflibercept for mCNV. Prompt treatment with these agents can lead to a better outcome.

Keywords: Intravitreal injection; aflibercept; ranibizumab; myopic choroidal neovascularization (mCNV)

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Introduction

Subfoveal myopic choroidal neovascularization (mCNV) can cause severe visual impairment in highly myopic patients (1). Photodynamic therapy with verteporfin (vPDT) was the first treatment approved for mCNV. The VIP study, a randomized controlled trial, has shown that vPDT can result in stabilization of vision following treatment at 1 year (2). At 2 years, the beneficial effects of vPDT were completely lost, as the difference in vision compared with placebo was no longer statistically significant (3). The long-term visual outcomes with vPDT for mCNV were even worse, with significantly decreased vision observed since 3 years after treatment (4). This may be because highly myopic eyes have preexisting retinal pigment epithelial atrophy, and vPDT further exacerbates the development of chorioretinal atrophy following treatment (5).

The pathophysiology of mCNV involves the presence of angiogenic stimulant regarding vascular endothelial growth factor (VEGF) (6). Intravitreal injections of anti-VEGF, including ranibizumab (7), bevacizuamb (8), pegaptanib (9), aflibercept (10) are proven to be effective for treating mCNV. The European Medicines Agency has approved intravitreal injections of ranibizumab for treating mCNV. Aflibercept is also approved in Japan for mCNV. Herein the clinical outcome of the randomized controlled studies in these approved pharmacotherapies will be reviewed.

Ranibizumab

Ranibizumab (Lucentis™, Genentech, Inc., South San

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Francisco, CA, USA and Novartis Pharma AG, Basel, Switzerland) is an antibody fragment with a high binding affinity towards all forms of VEGF-A, which can effectively inhibit intraocular level of VEGF-A. The RADIANCE study included 277 patients with visually impaired by mCNV, who were randomized to receive intravitreal ranibizumab 0.5 mg on day 1, month 1, and thereafter pro re nata (PRN) treatment guided by visual stabilization criteria; ranibizumab on day 1 and thereafter PRN regimen guided by disease activity criteria; or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (7). At month 3, ranibizumab resulted in a mean gain of nearly 10 letters, significantly better than vPDT in nearly 2 letters. The central retinal thickness also demonstrated significant decrease in the ranibizumab groups than in the vPDT group at month 3. Ranibizumab treatment guided by disease activity (11.7-letter visual gain) was non-inferior to visual stabilization-guided retreatment (11.9-letter visual gain) at month 6. With the allowance of ranibizumab after month 3 in the vPDT group, visual acuity greatly improved as nearly +9-letter, but still worse than ranibizumab group as 13 to 14 letters gain at month 12. At month 12, 63.8% to 65.7% of patients showed resolution of mCNV leakage. Patients received a median of 4.0 in visual-guided ranibizumab retreatment, and 2.0 ranibizumab injections in anatomical-guided ranibizumab over 12 months. No significant ocular or nonocular safety events were identified. The authors conclude ranibizumab is superior to vPDT for treating patients with mCNV, either retreatment according to visual stabilization or disease activity over 12-month period. Delayed ranibizumab treatment can lead to worse visual prognosis.

Recently, head-to-head comparison of two anti-VEGF agents for mCNV was published (8). The randomized study included 78 eyes with mCNV, who were randomized to receive intravitreal 1.25 mg bevacizumab or 0.5 mg ranibizumab. The injections were administered in PRN regimen. After mean 19-month follow-up, visual improvement was comparable between two groups. Multivariate analysis showed no influence of age or previous vPDT on final visual changes. The mean number of treatments in the first year was 2.7 in bevacizumab group and 2.3 in ranibizumab group, without clinically significant difference. The authors concluded bevacizumab and ranibizumab had similar efficacy and duration of action for treating mCNV.

Aflibercept

Aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) is a decoy receptor fusion protein, composed of the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2, which are fused to the Fc domain of human IgG1. Aflibercept can downregulate both VEGF-A and placental growth factor, which are synergistic for pathologic angiogenesis. The MYRROR study, a randomized controlled trial, demonstrated the efficacy of intravitreal aflibercept 2 mg over the sham injection for 121 patients with subfoveal or juxtafoveal mCNV (10). The authors used one injection at baseline then PRN treatment according to (I) reduction in visual acuity more than 5 letters from the previous visual examination; (II) central retinal thickness increases more than 50 μm from the previous optical coherence tomographic examination; (III) new or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment; (IV) new or persistent mCNV or bleeding. The 6-month results showed that the aflibercept group gained mean 12.1 letters, significantly better than the sham group having mean 2.0-letter loss. Decrease of central retinal thickness and mCNV size was more prominent in the aflibercept group than in the sham group. The sham group was allowed to receive PRN ranibizumab injections from month 6 to month 12. The 1-year results showed that despite visual improvement in 3.9 letters in the prior sham group after administration of aflibercept, still significantly worse than prior aflibercept group with 13.5-letter visual gain. The median number of prior aflibercept group was nearly two injections over 12 months, mostly before month 2. No significant ocular or nonocular safety events were observed except macular hole after aflibercept administration in one patient. The authors conclude aflibercept is superior to sham for managing mCNV. Delayed aflibercept treatment can lead to irreversible visual impairment.

Although there was no serious adverse effect reported in studies of ranibizumab and aflibercept for mCNV, some rare serious complications were found after use for other indications. Retinal pigment epithelium tears, macular ischemia, cataract progression, retinal breaks and detachment, endophthalmitis, macular hole, and intraocular inflammation were reported as ocular complications after intravitreal anti-VEGF for treating neovascular AMD (11). Systemic adverse effects were uncommonly reported such as thromboembolic events (stroke and myocardial infarction) and gastro-intestinal bleeding (12).

Conclusions

In summary, there are two approved pharmacotherapy for

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treating mCNV, ranibizumab and aflibercept, categorized as anti-VEGF agents. They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or vPDT. There is no severe ocular or systemic adverse reaction reported in studies associated with anti-VEGF for mCNV. Intravitreal anti-VEGF requires baseline one injection then PRN retreatment according to either visual acuity or anatomical changes. Prompt treatment with these agents can lead to a better outcome.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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