



The use of aflibercept in ophthalmology: a review of randomized controlled trials

Yen-Yi Chen¹, Pei-Yao Chang^{1,2}, Jia-Kang Wang^{1,2,3,4,5}

¹Department of Ophthalmology, Far Eastern Memorial Hospital, New Taipei City, Taiwan, China; ²Department of Medicine, National Taiwan University, Taipei City, Taiwan, China; ³Department of Medicine, National Yang Ming University, Taipei City, Taiwan, China; ⁴Department of Healthcare Administration and Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan, China; ⁵Department of Electrical Engineering, Yuan Ze University, Taoyuan City, Taiwan, China

Contributions: (I) Conception and design: YY Chen, JK Wang; (II) Administrative support: PY Chang; (III) Provision of study materials or patients: JK Wang; (IV) Collection and assembly of data: JK Wang; (V) Data analysis and interpretation: YY Chen, JK Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Jia-Kang Wang. Department of Ophthalmology, Far Eastern Memorial Hospital, 21, Sec. 2, Nan-Ya South Road, Pan-Chiao District, New Taipei City, 220, Taiwan, China. Email: jiakangw2158@gmail.com.

Abstract: We reviewed randomized controlled trials associated with the intravitreal use of aflibercept for this article. These studies proved that aflibercept is an effective anti-vascular endothelial growth factor agent for the treatment of neovascular age-related macular degeneration (nAMD), myopic choroidal neovascularization (mCNV), diabetic macular edema (DME), and macular edema associated with retinal vein occlusion. The incidence of severe ocular or systemic complications after intravitreal administration of aflibercept was low.

Keywords: Intravitreal injection; aflibercept; age-related macular degeneration; retinal vein occlusion; diabetic macular edema (DME); myopic choroidal neovascularization (mCNV)

Received: 31 August 2016; Accepted: 28 October 2016; Published: 13 February 2017.

doi: 10.21037/aes.2016.12.03

View this article at: <http://dx.doi.org/10.21037/aes.2016.12.03>

Introduction

Vascular endothelial growth factor (VEGF) is an angiogenic stimulant associated with the formation of choroidal neovascularization (1) and retinal neovascularization (2). VEGF can also induce macular edema by increasing vascular permeability (3). Aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) consists of the third domain of VEGF receptor 2, second domain of human VEGF receptor 1, and Fc domain of human immunoglobulin G1 (4). Aflibercept serves as a decoy to inactivate placental growth factor, VEGF-B, and VEGF-A, which are responsible for pathologic angiogenesis (5). The binding affinity of VEGF for this drug is higher than that for the VEGF-antagonists ranibizumab and bevacizumab (6). In comparison with ranibizumab and bevacizumab, aflibercept provides prolonged VEGF inhibition in retinal

pigment epithelium/choroid organ cultures (7). Intravitreal injection of aflibercept is an efficacious treatment for various macular diseases, including neovascular age-related macular degeneration (nAMD) (4,8), myopic choroidal neovascularization (mCNV) (9), diabetic macular edema (DME) (10,11), and macular edema associated with branch retinal vein occlusion (BRVO) (12) and central retinal vein occlusion (CRVO) (13,14).

A recent review of several randomized trials of intravitreal aflibercept administration in patients with nAMD, DME, and macular edema associated with BRVO and CRVO found that the rates of serious ocular adverse events such as intraocular inflammation and endophthalmitis were low and comparable to those of the controls (15). A prior randomized study found that throughout a 4-week observational period, intravitreal aflibercept caused significant reductions in systemic VEGF levels, which

may predispose patients to systemic adverse effects such as compromised wound-healing status, systemic hypertension, and arterial thromboembolic events (16). However, the incidence of serious systemic complications after intravitreal aflibercept was similar to those of controls and similar across various ocular indications (15). Herein, randomized controlled trials of intravitreal aflibercept for these macular disorders are reviewed to investigate the clinical efficacy and safety of this agent.

nAMD

Choroidal neovascularization in nAMD can cause severe visual impairment in aged patients. The pathophysiology of nAMD involves the presence of abnormal angiogenesis, mainly resulting from VEGF stimulation (1). Other anti-VEGF agents, such as bevacizumab (17), ranibizumab (17), and pegaptanib (18) have proven effective in managing nAMD. Two randomized controlled trials namely VIEW 1 and VIEW 2 examined 2,419 patients with active subfoveal or juxtafoveal choroidal neovascularization secondary to nAMD. The patients were randomized into groups to receive intravitreal aflibercept, 0.5 mg monthly (0.5q4); 2 mg monthly (2q4); 2 mg every 2 months after three initial monthly doses (2q8); or ranibizumab, 0.5 mg monthly. Mean visual gains, subjective visual function according to a self-reported questionnaire, and reduction of central retinal thickness from baseline to 1 year were comparable between the aflibercept 2q4 and ranibizumab ($P>0.05$), aflibercept 2q8 and ranibizumab ($P>0.05$), and aflibercept 0.5q4 and ranibizumab ($P>0.05$) groups (4,19). However, the resolution of intraretinal cystoid fluid, subretinal fluid, and pigment epithelial detachment was consistently more significant in the groups receiving monthly aflibercept compared with those receiving bimonthly aflibercept or ranibizumab (20).

From months 12 to 24, all patients received PRN treatments. Retreatment criteria were the presence of new or persistent fluid observed with optical coherence tomography, an increase in central retinal thickness of more than 100 μm , the loss of visual acuity for more than five letters, the development of new-onset classic neovascularization, the presence of a new or persistent leak observed with fluorescein angiography, the development of a new macular hemorrhage, or a time lapse of 12 weeks since the previous injection. The visual results at 2 years were +6.6- to +7.6-letter gains compared with baseline in the aflibercept groups and noninferior to +7.9-letter gains

in the ranibizumab group ($P>0.05$) (8). However, small losses in visual improvement were observed at 2 years compared with visual gains at 1 year. We suggest that compared with scheduled treatment during the first year, PRN injections during the second year may cause less stable visual outcomes (21). Patients in the aflibercept 2q8 group received an average of 11.2 injections over 2 years, which was fewer than the 16.5 injections administered in the ranibizumab group ($P<0.0001$).

Severe ocular adverse events were similar across groups (3.2–4.4%) over 2 years and included elevated intraocular pressure, cataract aggravation, tears in the retinal pigment epithelium, retinal hemorrhage, retinal detachment or associated tears, and endophthalmitis. Systemic serious adverse reactions were mainly arterial thromboembolic events (stroke and myocardial infarction) and were similar across groups (2.4–3.8%) over 2 years. The authors concluded that significant and equal visual improvement can be achieved after either aflibercept or ranibizumab administration in patients with nAMD within 2 years of treatment. In intravitreal aflibercept, lesser number of injections were found (initially 3-monthly loading, followed by every 2 months injections within 1 year, and PRN or mandatory doing every 3 months between 1 to 2 years) than in ranibizumab (monthly injections for year 1 and PRN or mandatory doing every 3 months between 1 and 2 years).

Intravitreal administration of aflibercept and ranibizumab was concluded to be safe owing to the low incidence of ocular and systemic serious adverse events reported during the 2-year study period. Intravitreal aflibercept for treating nAMD has been approved by the European Medicines Agency (EMA) and the Food and Drug Administrations (FDAs) of the United States and Taiwan.

mCNV

Subfoveal mCNV can cause severe visual impairment in patients with high myopia (22) and is associated with the presence of VEGF (23). The intravitreal administration of the anti-VEGF composing of ranibizumab (24), bevacizumab (25), and pegaptanib (26) are effective for managing mCNV. The MYRROR study (9) included 121 patients with subfoveal or juxtafoveal mCNV who were randomly assigned to receive intravitreal injection of aflibercept (2 mg) or sham treatment. The 2 mg dose of aflibercept was approved by the FDA and EMA; therefore, 0.5 mg aflibercept was not considered as another arm for the study. The authors used one injection at baseline followed

by PRN treatment according to the following points: (I) reduction in visual acuity of more than 5 letters from the previous visual examination; (II) central retinal thickness increase of more than 50 μm from the previous optical coherence tomographic examination; (III) the presence of new or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment; and (IV) the development of new or persistent mCNV or bleeding.

A mean 12.1-letter improvement was achieved after 6 months following aflibercept therapy, a result significantly superior to the mean 2-letter decrease in the sham group. Compared with the sham group, the aflibercept group showed a more prominent decrease in central retinal thickness and mCNV size. Ranibizumab PRN injections were administered in the sham group from months 6 to 12. The 1-year results showed that despite a visual improvement of 3.9 letters after receiving aflibercept treatment, the outcome of patients in the sham group was still significantly worse than that in the aflibercept group, in which patients showed a mean 13.5-letter visual gain.

The median number of injections administered to the original aflibercept group was nearly two injections over 12 months, mostly before month 2. Ocular or systemic severe adverse events were not observed except for the development of a macular hole after aflibercept administration in one patient. The authors concluded that aflibercept is superior to no treatment in the management of mCNV and that delayed aflibercept treatment can lead to irreversible visual impairment. Aflibercept has been approved to treat mCNV in Japan.

DME

Macular edema is a threat to vision in patients with diabetes. Both the inflammation and the abnormal angiogenesis associated with VEGF can induce the formation of DME (3). Intraocular treatment with anti-VEGF agents, including ranibizumab (27), bevacizumab (28), and pegaptanib (29), are effective in managing DME. The DA VINCI study, a phase-II randomized controlled trial, examined 221 patients with diabetes and center-involving macular edema (10). The patients were randomized into groups to receive macular laser photocoagulation or intravitreal aflibercept, 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after three initial monthly doses (2q8), or 2 mg PRN after three initial monthly doses (2PRN).

Mean visual gains from baseline to 1 year were +11.0, +13.1, +9.7, and +12.0 letters for the aflibercept 0.5q4,

2q4, 2q8, and 2PRN regimens, respectively, which was significantly superior to the -1.3-letter outcome for the laser group. Central retinal thickness reduction in the laser group was smaller than that in the aflibercept groups. Compared with laser treatment, intravitreal aflibercept also significantly improved retinal sensitivity as assessed by microperimetry (30).

The VISTA and VIVID randomized studies compared the clinical outcomes of macular grid laser treatment with the administration of intravitreal aflibercept (2 mg) in 872 patients with center-involving DME for 1 year (11). Patients in the VISTA study initially received five continuous monthly injections and were then treated every 4 weeks (2q4) or every 8 weeks (2q8). Mean visual gains from baseline to 2 years were +11.5 and +11 letters in the aflibercept 2q4 and 2q8 groups, respectively. This outcome was significantly superior to the +0.9-letter improvement observed in the laser-only group. Mean visual gains in the VIVID study at 1 year were similar, +11.4 and +9.4 letters in the aflibercept 2q4 and 2q8 groups, respectively. This outcome was significantly superior to the +0.7-letter improvement in the laser group. Compared with the laser group, the aflibercept groups showed more profound reductions in central retinal thickness without serious systemic or ocular adverse effects. Compared with laser therapy, aflibercept therapy resulted in significantly greater reduction in the severity of diabetic retinopathy in patients with DME.

A post hoc analysis divided patients with DME in the VISTA study into subgroups of patients with and without prior anti-VEGF treatments including bevacizumab in most patients and ranibizumab in the minority of patients (31). In comparison with the laser treatment, intravitreal aflibercept resulted in significant and similar visual and anatomic improvements at the end of 2 years in subgroups with and without prior anti-VEGF therapies. The author concluded that compared with conventional macular laser therapy, aflibercept provided safe and superior treatment outcomes in patients with DME and even concomitant diabetic retinopathy. The FDAs in the United States and Taiwan and the EMA have approved intravitreal injections of aflibercept for the treatment of DME.

A comparison of three anti-VEGF agents in the treatment of DME was also recently published. The randomized controlled study included 660 eyes with center-involving DME that were randomized to receive intravitreal treatments of 2 mg aflibercept, 1.25 mg bevacizumab, or 0.3 mg ranibizumab. The injections were administered every 4 weeks until improvement ceased and treatment

then resumed if symptoms worsened. The 1-year results demonstrated that all three anti-VEGF agents improved vision in the eyes of diabetic patients with macular edema (32). When baseline visual loss was mild (visual acuity from 69 to 78 letters), visual gains were similar between all groups. At lower levels of initial visual acuity (less than 69 letters), aflibercept was more effective than the other agents in improving vision. No significant differences were found among the treatment groups in the rates of serious adverse events or major cardiovascular events.

Outcomes at 2 years for these eyes with center-involved DME showed significant visual improvement with all three anti-VEGF agents for these eyes with center-involved DME (33). The median injection number decreased from approximately 9–10 injections during years 1–5 to 6 injections during year 2 in all three groups. Among eyes with lower baseline visual acuity, aflibercept gave 2-year visual outcomes superior to those of bevacizumab, but the superiority of aflibercept over ranibizumab that was noted at year 1 was no longer observed at 2 years.

Macular edema associated with retinal vein occlusion

Macular edema secondary to BRVO commonly impairs vision and is associated with the presence of VEGF (34,35). Ranibizumab (36), bevacizumab (37), and pegaptanib (38) have been effective in treating macular edema in patients with BRVO. The VIBRANT study randomly distributed 181 patients with macular edema in BRVO into groups receiving treatment with intravitreal aflibercept (2 mg) or macular grid laser and followed them for 1 year (12). Aflibercept was injected 6 monthly intervals at the start of the study. At month 6, a mean 6.9-letter gain was observed in the laser group, which was significantly worse than the mean 17-letter improvement in the aflibercept group. Compared with laser therapy, aflibercept treatment resulted in a greater reduction in macular thickness.

From months 6 to 12, patients in the aflibercept group received injections every 8 weeks, and those in the laser group were administered rescue therapy of aflibercept with 3 initial monthly doses followed by injections every 8 weeks. The mean changes from baseline visual acuity and central retinal thickness were still significantly better in the aflibercept group (+17.1 letters and $-283.9\ \mu\text{m}$) than in laser/aflibercept group (+12.2 letters and $-249.3\ \mu\text{m}$). No accompanying serious ocular or systemic adverse events were observed through 1 year of follow-up. The authors concluded that

aflibercept allowed superior control of macular edema associated with BRVO than laser. Delayed aflibercept treatment in the initial laser group achieved substantial visual improvement, but these improvements were inferior to those achieved with early aflibercept therapy. The FDAs in the United States and Taiwan have approved intravitreal injections of aflibercept for the treatment of macular edema originating from BRVO.

Macular edema can also cause severe visual depression in patients with CRVO (34), and the pathogenesis of macular edema secondary to CRVO is associated with VEGF (35). Macular edema resulting from CRVO can be effectively managed with intravitreal injections of anti-VEGF agents such as ranibizumab (39), bevacizumab (40), and pegaptanib (41). The randomized COPERNICUS and GALILEO studies compared the outcome of intravitreal aflibercept administration with sham injection for the treatment of macular edema associated with CRVO (13,14). The authors in the COPERNICUS study administered monthly aflibercept to 114 patients and sham injections to 74 patients for the first 6 months of the study (13). At month 6, visual improvement from baseline was significantly greater in the aflibercept group, with a mean +17.3-letter gain compared with a mean 4-letter loss in the sham group. From months 6 to 24, all patients received PRN aflibercept injections. At the end of 2 years, the results in the original aflibercept group (mean +13-letter gain) were superior to those in the original sham group (mean +1.5-letter gain).

The GALILEO study compared the effects of six monthly aflibercept injections followed by PRN injections in 106 patients with those of sham injections in 71 patients for the first year of the study (14). After 12 months of follow-up, a mean 3.8-letter improvement was observed in the sham group. This outcome was significantly worse than the mean 16.9-letter gain observed in the aflibercept group. From months 12 to 18, all patients received PRN aflibercept injections. At month 18, the original aflibercept group showed better results, with a mean +13.7-letter gain compared with the mean +6.2-letter gain in the original sham group.

Anatomical improvement in central retinal thickness after aflibercept therapy was noted in these two trials, and severe ocular and systemic complications after aflibercept injections were rarely reported. The authors concluded that aflibercept administration is superior to no treatment for the management of macular edema associated with CRVO and that early aflibercept treatment can lead to superior visual improvement. The FDAs in the United States and

Taiwan and the EMA have approved intravitreal injections of aflibercept for the treatment of macular edema secondary to CRVO.

Conclusions

Intravitreal aflibercept has been approved as an effective and safe anti-VEGF agent for the treatment of nAMD, mCNV, DME, and macular edema secondary to retinal vein occlusion. Aflibercept is as effective as ranibizumab, another anti-VEGF for treating nAMD and DME. Compared with conventional macular laser treatment, aflibercept treatment results in greater improvements in the symptoms of DME and macular edema with BRVO. Aflibercept is also more efficacious than sham treatment in managing mCNV and macular edema secondary to CRVO. Serious ocular or systemic complications associated with the intravitreal administration of aflibercept occur only rarely. Compared with immediate aflibercept injection, delayed treatment can result in worse outcomes. Repeat injections and the close monitoring of anatomical and visual changes are essential during aflibercept treatment.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aes.2016.12.03>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Barouch FC, Miller JW. Anti-vascular endothelial growth factor strategies for the treatment of choroidal neovascularization from age-related macular degeneration. *Int Ophthalmol Clin* 2004;44:23-32.
2. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 1994;118:445-50.
3. Funatsu H, Yamashita H, Ikeda T, et al. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. *Ophthalmology* 2003;110:1690-6.
4. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119:2537-48.
5. Castellon R, Hamdi HK, Sacero I, et al. Effects of angiogenic growth factor combinations on retinal endothelial cells. *Exp Eye Res* 2002;74:523-35.
6. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012;15:171-85.
7. Klettner A, Recher M, Roeder J. Comparison of the efficacy of aflibercept, ranibizumab, and bevacizumab in an RPE/choroid organ culture. *Graefes Arch Clin Exp Ophthalmol* 2014;252:1593-8.
8. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014;121:193-201.
9. Ikuno Y, Ohno-Matsui K, Wong TY, et al. Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularization: The MYRROR Study. *Ophthalmology* 2015;122:1220-7.
10. Do DV, Nguyen QD, Boyer D, et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 2012;119:1658-65.
11. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. *Ophthalmology* 2015;122:2044-52.
12. Clark WL, Boyer DS, Heier JS, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-Week Results of the VIBRANT Study. *Ophthalmology* 2016;123:330-6.
13. Heier JS, Clark WL, Boyer DS, et al. Intravitreal

- afibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. *Ophthalmology* 2014;121:1414-1420.e1.
14. Ogura Y, Roider J, Korobelnik JF, et al. Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 GALILEO study. *Am J Ophthalmol* 2014;158:1032-8.
 15. Kitchens JW, Do DV, Boyer DS, et al. Comprehensive Review of Ocular and Systemic Safety Events with Intravitreal Aflibercept Injection in Randomized Controlled Trials. *Ophthalmology* 2016;123:1511-20.
 16. Zehetner C, Kralinger MT, Modi YS, et al. Systemic levels of vascular endothelial growth factor before and after intravitreal injection of aflibercept or ranibizumab in patients with age-related macular degeneration: a randomised, prospective trial. *Acta Ophthalmol* 2015;93:e154-9.
 17. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388-98.
 18. Singerman LJ, Masonson H, Patel M, et al. Pegaptanib sodium for neovascular age-related macular degeneration: third-year safety results of the VEGF Inhibition Study in Ocular Neovascularisation (VISION) trial. *Br J Ophthalmol* 2008;92:1606-11.
 19. Yuzawa M, Fujita K, Wittrup-Jensen KU, et al. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. *Ophthalmology* 2015;122:571-8.
 20. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and Visual Acuity in Aflibercept and Ranibizumab Therapy for Neovascular Age-Related Macular Degeneration in the VIEW Trials. *Ophthalmology* 2016;123:1521-9.
 21. Richard G, Monés J, Wolf S, et al. Scheduled versus Pro Re Nata Dosing in the VIEW Trials. *Ophthalmology* 2015;122:2497-503.
 22. Secrétan M, Kuhn D, Soubrane G, et al. Long-term visual outcome of choroidal neovascularization in pathologic myopia: natural history and laser treatment. *Eur J Ophthalmol* 1997;7:307-16.
 23. Yamamoto Y, Miyazaki D, Sasaki S, et al. Associations of inflammatory cytokines with choroidal neovascularization in highly myopic eyes. *Retina* 2015;35:344-50.
 24. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology* 2014;121:682-92.e2.
 25. Pece A, Milani P, Monteleone C, et al. De Crecchio G5, A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV. *Graefes Arch Clin Exp Ophthalmol* 2015;253:1867-72.
 26. Rinaldi M, Chiosi F, Dell'Omo R, et al. Intravitreal pegaptanib sodium (Macugen) for treatment of myopic choroidal neovascularization: a morphologic and functional study. *Retina* 2013;33:397-402.
 27. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013;120:2013-22.
 28. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3 *Arch Ophthalmol* 2012;130:972-9.
 29. Sultan MB, Zhou D, Loftus J, et al. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology* 2011;118:1107-18.
 30. Gonzalez VH, Boyer DS, Schmidt-Erfurth U, et al. Microperimetric assessment of retinal sensitivity in eyes with diabetic macular edema from a phase 2 study of intravitreal aflibercept. *Retina* 2015;35:687-94.
 31. Do DV, Nguyen QD, Vitti R, et al. Intravitreal Aflibercept Injection in Diabetic Macular Edema Patients with and without Prior Anti-Vascular Endothelial Growth Factor Treatment: Outcomes from the Phase 3 Program. *Ophthalmology* 2016;123:850-7.
 32. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193-203.
 33. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology* 2016;123:1351-9.
 34. Hahn P, Fekrat S. Best practices for treatment of retinal vein occlusion. *Curr Opin Ophthalmol* 2012;23:175-81.
 35. Stewart MW. The expanding role of vascular endothelial growth factor inhibitors in ophthalmology. *Mayo Clin*

- Proc 2012;87:77-88.
36. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology* 2011;118:1594-602.
 37. Russo V, Barone A, Conte E, et al. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. *Retina* 2009;29:511-5.
 38. Wroblewski JJ, Wells JA 3rd, Gonzales CR. Pegaptanib sodium for macular edema secondary to branch retinal vein occlusion. *Am J Ophthalmol* 2010;149:147-54.
 39. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology* 2011;118:2041-9.
 40. Epstein DL, Algvere PV, von Wendt G, et al. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. *Ophthalmology* 2012;119:2587-91.
 41. Wroblewski JJ, Wells JA 3rd, Adamis AP, et al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. *Arch Ophthalmol* 2009;127:374-80.

doi: 10.21037/aes.2016.12.03

Cite this article as: Chen YY, Chang PY, Wang JK. The use of aflibercept in ophthalmology: a review of randomized controlled trials. *Ann Eye Sci* 2017;2:12.