Curr Ophthalmol Rep (2013) 1:122–127
DOI 10.1007/s40135-013-0018-0

Anti-VEGF Therapy for the Management of Diabetic Macular Edema

Marianeli Rodriguez · Philip Storey · Diana V. Do

Published online: 25 July 2013

Abstract To review the medical evidence for the use of intravitreal vascular endothelial growth factor (VEGF) inhibitors for the treatment of diabetic macular edema (DME). Evaluation of randomized clinical trials evaluating VEGF inhibitors for center-involved DME. Ranibizumab, an anti-VEGF antibody fragment, was evaluated in two phase III clinical studies entitled RISE and RIDE. At 24 months, significantly more ranibizumab treated patients gained ≥15 letters in vision as compared to the sham group (44.8 and 39.2 % vs. 18.1 %; $P < 0.0001$). The ranibizumab group improved a mean of 250.6–270.7 μm in central foveal thickness compared to a mean improvement of 125.8–133.4 μm for the sham group. In addition, ranibizumab treated patients were more likely to have improvement in retinopathy. Additional clinical trials have evaluated bevacizumab, another anti-VEGF antibody fragment, and aflibercept, a fusion protein that blocks VEGF. Both bevacizumab and aflibercept have also resulted in superior visual acuity outcomes compared to focal laser photocoagulation. All three agents appear to be safe though these clinical trials were not powered to evaluate safety as a primary outcome. Recent clinical trials have demonstrated the superior outcomes with anti-VEGF agents compared to laser alone or sham treatment. Bevacizumab, ranibizumab and aflibercept have all shown remarkable improvements in both visual acuity outcomes and retinal thickness reductions.

M. Rodriguez · P. Storey
The Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

D. V. Do (✉)
The Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, NE, USA
e-mail: diana.do@unmc.edu

Keywords Diabetes · Diabetic macular edema · Anti-VEGF · Pegaptanib · Ranibizumab · Bevacizumab · Aflibercept

Introduction

Diabetic maculopathy causes the majority of visual loss in patients with diabetic retinopathy [1]. The Wisconsin epidemiologic study of diabetic retinopathy (WESDR) reported a 98 % rate of retinopathy in Americans with type 1 diabetes with the disease for more than 15 years and a rate of 78 % for Americans with type 2 diabetes [2]. The WESDR reported a 28 % prevalence of diabetic macular edema (DME) 20 years after initial diagnosis of type 1 or 2 diabetes [3]. With the prevalence of diabetes mellitus expected to increase from 180 million people to 300 million people worldwide by 2025, diabetic retinopathy and macular edema will become more prevalent as well [4].

For over 20 years, focal laser photocoagulation remained the standard of care for clinically significant macular edema (CSME) based on the results of the Early Treatment Diabetic Retinopathy Study (ETDRS), which showed a 50 % reduction in moderate vision loss over time compared with untreated patients [5]. However, few patients in the ETDRS experienced significant improvement in visual function and improvements tended to occur slowly. One possible explanation for this fact is that many patients in ETDRS started with good vision. Nevertheless, a treatment that both halted loss of visual acuity and can improve visual function has been greatly desired. Our understanding of the pathogenesis of DME has grown exponentially in recent years, allowing for the introduction of new treatment modalities. Intravitreal blockade of

vascular endothelial growth factor (VEGF), which has been applied successfully in the treatment of the wet form of age-related macular degeneration (AMD), has recently become integral in the management of DME. The focus of this chapter is to review the current evidence for the use of anti-VEGF medications in the treatment of DME, and to discuss some of the questions that remain to be answered with regards to these novel therapies (Table 1).

Diagnosing Diabetic Macular Edema (DME)

Slit-lamp biomicroscopy using a macular contact lens has been a useful method to detect clinically significant DME. In addition, stereo fundus photography with 30° images of the macula can help diagnose clinically significant DME.

Fluorescein angiography (FA) and optical coherence tomography (OCT) are two imaging modalities that are also important in determining the severity of the maculopathy [6, 7]. FA is useful in evaluating the pattern of fluid leakage and the presence of ischemia. OCT is helpful in detecting the extent of retinal thickness and to determine if vitreomacular traction or epiretinal membranes are also contributing to the edema [7, 8]. OCT has especially become key in tracking the response of patients to pharmacologic anti-VEGF therapies.

Table 1 Major DME treatment studies

Study	Medication	Subjects	Mean change in BCVA	Primary outcome
RISE	(1) 0.3 mg ranibizumab (2) 0.5 mg ranibizumab (3) Sham + laser	377 eyes, 377 patients	2-years 0.3 mg: +12.5 0.5 mg: +11.9 Sham + laser: +2.6	At 1 and 2 years, significantly more ranibizumab-treated patients gained ≥15 letters than sham-treated patients
RIDE	(1) 0.3 mg ranibizumab (2) 0.5 mg ranibizumab (3) Sham + laser	382 eyes, 382 patients	2-years 0.3 mg: +10.9 0.5 mg: +12.0 Sham + laser: +2.6	At 1 and 2 years, significantly more ranibizumab-treated patients gained ≥15 letters than sham-treated patients
BOLT	(1) 1.25 mg bevacizumab (2) Laser	80 eyes, 80 patients	1-year Bevacizumab: + 8.0 Laser: −0.5 2-years Bevacizumab: +8.6 Laser: −0.5	At 1 and 2 years, eyes randomized to ranibizumab had superior visual acuity compared to the laser group
DA VINCI	(1) 0.5 mg aflibercept q4 weeks (2) 2 mg aflibercept q4 weeks (3) 2 mg aflibercept for 3 months then q8 weeks (4) 2 mg aflibercept for 3 months then PRN (5) Laser	221 eyes, 221 patients	1-year 0.5q4: +11.0 2q4: +13.2 2q8: +9.7 2PRN: +12.0 Laser: −1.3	At 1 year, all 4 aflibercept groups had superior improvements in visual acuity and superior reduction in central retinal thickness compared to the laser group
DRCR	(1) 0.5 mg ranibizumab + prompt laser (2) 0.5 mg ranibizumab + deferred laser (3) 4 mg triamcinolone + prompt laser (4) Sham + prompt laser	854 eyes 691 patients	1-year Ranibiz + prompt: +9 Ranibiz + deferred: +9 Triam + prompt: +4 Sham + prompt: +3 2-years Ranibiz + prompt: +7 Ranibiz + deferred: +9 Triam + prompt: +2 Sham + prompt: +3	At 1 and 2 years, mean number of letters gained was significantly higher for the ranibizumab + prompt or deferred laser but not in the triamcinolone + prompt laser group compared to the sham + prompt laser group
DRCR	2.0 mg aflibercept 1.25 mg bevacizumab 0.3 mg ranibizumab	Target: 660 eyes	Pending	Pending

The ETDRS trial defined CSME as one of the following: retinal thickening within 500 um of the macular center, presence of hard exudates within 500 μm of the macular center if there is adjacent retinal thickening, or zone(s) of retinal thickening within one disk diameter that is at least one disk area in size themselves [9]. Focal or diffuse is often used to describe the pattern of leakage on FA. In focal DME there are discrete areas of leakage noted on FA that correspond to leaking microaneurysms [10]. Diffuse DME results from a generalized breakdown of the blood retinal barrier (BRB) and often appears as leakage on FA that is not associated with microaneurysm [11].

Role of VEGF in the Pathogenesis of DME

Chronic hyperglycemia leads to the accumulation of advanced glycation end products (AGEs) on the amino groups of proteins, leading to disruptions in the native structure and function of those proteins [12]. AGEs are associated with the neovascular injury occurring in diabetic retinopathy through several mechanisms: they lead to phenotypic changes of glial cells whose processes surround the retinal vascular endothelial cells [13], they promote leukostasis which is related to loss of pericytes, the microvascular mural cells that stabilize the inner BRB [14], and they also modify the expression of VEGF, one of the most potent angiogenesis-inducing factors [15, 16].

Numerous studies have demonstrated that VEGF is a major factor in mediating increased vascular permeability in the retina by inducing conformational changes in the tight junctions of the vascular endothelial cells [17, 18]. Interestingly, when VEGF is administered to rats, capillary and post-capillary venule permeability increases rapidly [19]. Moreover, intraocular VEGF levels have been found to be higher in patients with diabetes than without the disease [20] and animal models of non-proliferative diabetic retinopathy show increased retinal VEGF levels and VEGF receptor 2 (R2) expression [21]. VEGF has also been shown to promote inflammatory cell migration that leads to endothelial cell apoptosis in the retinal vasculature [22]. Taken these results together, a new picture has emerged in our understanding of the pathogenesis of DME, with AGEs as the initiators of microvascular damage, VEGF as a perpetrator of the insult by promoting the growth of new and leaky vessels, and the final result a breakdown of the BRB and accumulation of fluid within the retina. Our deeper understanding of this process has led to the development of new therapies to manage DME. Specifically, anti-VEGF agents are emerging as a new standard of care in the treatment of DME because of their efficacy in treating this condition.

VEGF Antibodies

Bevacizumab

Bevacizumab (Avastin; Genentech Inc) is a monoclonal antibody that competitively inhibits all isoforms of the VEGF-A family. A number of retrospective uncontrolled case series with variable treatment regimens have indicated that intravitreal bevacizumab has a beneficial effect on DME [23–26]. Prospective, randomized, controlled trials have revealed the most reliable data concerning the beneficial effects of bevacizumab in DME. The strongest evidence to date of the effect of bevacizumab in DME comes from a prospective randomized trial entitled BOLT (intravitreal bevacizumab or laser therapy in the management of diabetic macular edema) [27••]. Eighty eyes from 80 patients with persistent clinically significant diabetic macular edema were randomized to either intravitreal bevacizumab (median of 13 treatments) or macular laser therapy (median of 4 treatments). The primary end point was the difference in best-corrected visual acuity (BCVA) from baseline between the bevacizumab and laser groups. At the end of 24 months, eyes randomized to bevacizumab had superior visual acuity (64.4 vs. 54.8 ETDRS BCVA) with a mean gain of 8.6 ETDRS letters compared to the laser therapy group, which lost a mean of 0.5 letters ($P = 0.005$). Ocular and systemic serious adverse events (SAE) were both minimal and similarly distributed between the bevacizumab (3 SAE's) and laser treatment (7 SAE's) groups.

Ranibizumab

Ranibizumab (Lucentis, Genentech Inc) is an affinity matured, anti-VEGF antibody fragment (Fab fragment) that neutralizes the activity of all known active isoforms of VEGF-A and was FDA-approved for the treatment of DME at the dose of 0.3 mg in April 2012 [28]. Evaluation of ranibizumab in DME comes from two 24-month phase III clinical studies entitled RISE and RIDE [29••]. The studies randomized patients to monthly intravitreal injections of 0.3 mg ranibizumab, 0.5 mg ranibizumab or a sham injection. Beginning at 3 months, ophthalmologists assessed all patients for the need for macular laser according to protocol-specified criteria. In RISE, 377 patients were enrolled. At 24 months, significantly more ranibizumab treated patients gained ≥15 letters in vision as compared to the sham group (44.8 and 39.2 % vs. 18.1 %; $P < 0.0001$). In RIDE, 382 patients were randomized and more ranibizumab treated patients also gained ≥15 letters in vision (33.6 and 45.7 % vs. 12.3 %; $P < 0.0001$). Ranibizumab treated patients had fewer macular laser procedures over

24 months (mean of 1.8 and 1.6 procedures in sham patients vs. 0.3–0.8 in treatment patients) and significant improvements in macular edema on OCT. At 24 months, the ranibizumab group improved a mean of 250.6–270.7 μm in central foveal thickness compared to a mean improvement of 125.8–133.4 μm for the sham group. In addition, ranibizumab treated patients were more likely to have improvement in retinopathy.

SAE were rare. Vitreous hemorrhage was the most common ocular SAE, occurring in a total of 7 sham-treated eyes and 2 ranibizumab treated eyes. Out of the 10,584 intravitreal injections, other ocular SAE were also rare: 4 cases of endophthalmitis, 3 cases of traumatic cataract and 1 rhegmatogenous retinal detachment. Deaths of vascular or unknown cause as well as cerebrovascular accidents were slightly more common in patients treated with ranibizumab. The sham group had 1 (0.8 %) and 2 (1.6 %) total deaths compared to 3 (2.4 %) and 4 (3.2 %) for the 0.3 mg ranibizumab group and 5 (4.0 %) and 6 (4.8 %) in the 0.5 mg ranibizumab group.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a randomized controlled trial of 854 eyes evaluating the comparative effectiveness of 4 different treatments for center-involving DME: intravitreal 0.5 mg ranibizumab combined with prompt focal/grid laser; 0.5 mg ranibizumab combined with deferred (≥24 weeks) focal/grid laser; 4 mg triamcinolone combined with prompt focal/grid laser; or sham injections with prompt focal/grid laser alone [30••]. At 1 year, the mean number of letters gained ± standard deviation was significantly greater in the ranibizumab + prompt laser group (+9 ± 11, $P < 0.001$) and ranibizumab + deferred laser group (+9 ± 12, $P < 0.001$) but not in the triamcinolone + prompt laser group (+4 ± 13, $P = 0.31$) compared to the sham + prompt laser group (+3 ± 13). Visual acuity outcomes at the 1-year visit were largely sustained through the 2 year visit in the ranibizumab arms. At 2 years, the mean number of letters gained ± standard deviation was significantly greater in the ranibizumab + prompt laser group (+7 ± 13, $P = 0.03$) and ranibizumab + deferred laser group (+9 ± 14, $P < 0.001$) but not in the triamcinolone + prompt laser group (+2 ± 19, $P = 0.35$) compared to the sham + prompt laser group (+3 ± 15). At 2-years, the percentage of eyes with central foveal thickness ≥250 μm was 59 % for the sham plus deferred laser group, 43 % for the ranibizumab plus prompt laser group, 42 % for the ranibizumab plus deferred laser group, and 52 % for the triamcinolone plus prompt laser group. There were no systemic adverse events attributed to the treatments. Three patients (0.8 %) had post-injection endophthalmitis in the ranibizumab groups while cataract surgery and elevated intraocular pressure was more common in the triamcinolone group.

Aflibercept

Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc), also known as VEGF Trap-Eye, is a recombinant fusion protein made from a combination of two VEGF binding domains from human VEGF receptors 1 and 2 fused to the Fc domain of a human immunoglobulin [31]. In addition to binding VEGF-A and VEGF-B, aflibercept also binds placental growth factors 1 and 2, which have been shown to contribute to retinal neovascularization and excess vascular permeability [32]. Animal studies have revealed that aflibercept has a longer intra-ocular half-life and a higher binding affinity to VEGF-A than ranibizumab and bevacizumab, giving the drug a potential advantage over current therapies [33]. After a pilot study showed that a single intravitreal injection of aflibercept improved visual acuity and reduced retinal thickness in eyes with DME [34], a 24-week phase 2 multicenter randomized controlled study entitled DA VINCI (DME and VEGF Trap-Eye: Investigation of Clinical Impact) was undertaken, which gives the most thorough evaluation of VEGF Trap-Eye to date [35••].

In the DA VINCI study, a total of 221 diabetic patients with clinically significant DME involving the central macula (central retinal thickness ≥ 250 μm) were randomized to one of five groups: 0.5 mg aflibercept every 4 weeks; 2 mg aflibercept every 4 weeks; 2 mg aflibercept for 3 initial monthly doses and then every 8 weeks; 2 mg aflibercept for 3 initial monthly does and then on an as needed basis; or macular laser photocoagulation by the ETDRS protocol. Compared to the laser-treated group, all 4 aflibercept groups had superior improvements in visual acuity (range of +8.5 to +11.4 ETDRS letters vs. +2.5 letters in the laser group; $P \leq 0.0085$) and superior reduction in central retinal thickness (range of −127.3 to −194.5 μm vs. −67.9 μm in the laser group; $P = 0.0066$). While the study was not powered to detect differences in aflibercept treatment groups, there did not appear to be a substantial difference among the 4 groups in terms of visual acuity or central retinal thickness, which supports the notion that the longer intraocular half-life of aflibercept could result in a greater length of time between injections. Serious ocular adverse events were similar to previous studies of other intravitreal anti-VEGF drugs with two study patients having endophthalmitis. There was no evidence of increased serious systemic adverse events. A phase 3 clinical study in DME with aflibercept is currently ongoing.

Comparison of Anti-VEGF Agents

One of the remaining questions in the field of anti-VEGF treatment for DME is whether all the available agents provide the same efficacy in management of this condition. A

recent trial of 1,208 patients demonstrated that bevacizumab and ranibizumab had equivalent effects on visual acuity for the treatment of neovascular AMD [36•]. Although some may assume that based on this study both therapies would also be equally effective in the management of DME, there is no strong evidence supporting this assumption.

In August 2012, the DRCR network began enrolling patients in a randomized controlled trial evaluating 0.3 mg intravitreal ranibizumab, 1.25 mg bevacizumab or 2.0 mg aflibercept for the treatment of central involving DME. The study will include 660 eyes followed for 2-years and has a primary efficacy outcome of change in visual acuity from baseline to 1 year.

Conclusions

Since 2005, a host of clinical trials have investigated the potential use of anti-VEGF agents for diabetic macular edema. While macular laser has remained the standard of care for control groups in trials, the mounting evidences of superior outcomes in anti-VEGF treated patients has created a dramatic change in DME care.

Bevacizumab, ranibizumab and aflibercept have all shown remarkable improvements in both functional and anatomical terms. While it is tempting to compare effect size between trials, the variations in study group characteristics, treatment regimens, and study length makes it difficult to draw strong conclusions with regards to the relative benefit of one agent over another one. There remains a need for direct comparison of agent effectiveness, and hopefully the DRCR network clinical trial will provide ophthalmologists with important information on choosing the best treatment for our patients.

In addition to determining which anti-VEGF agent is most effective, the ideal dosage and timing of each agent also remains an unanswered question. A number of trials have included multiple treatment arms using different dosages of medication [29••, 35••, 37]. However, no trial has been sufficiently powered to draw firm conclusions concerning superiority of dosage or timing strategies. While recent trials have shed much light on the vast potential of anti-VEGF agents in DME, we eagerly await the results of additional clinical trials to further assist us in effectively treating patients with DME.

Disclosure Marianeli Rodriguez and Philip Storey declare that they have no conflict of interest. Diana V. Do has received research funding from Genentech and Regeneron.

References

Recent papers of particular interest have been highlighted as:

- • Of importance
- •• Of major importance

1. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther. 2008;88(11):1254–64.
2. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984;102(4):527–32.
3. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology. 1984;91(12):1464–74.
4. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21(9):1414–31.
5. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796–806.
6. Kang SW, Park CY, Ham DI. The correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema. Am J Ophthalmol. 2004;137(2):313–22.
7. Gaucher D, Tadayoni R, Erginay A, et al. Optical coherence tomography assessment of the vitreoretinal relationship in diabetic macular edema. Am J Ophthalmol. 2005;139(5):807–13.
8. Smith RT, Lee CM, Charles HC, et al. Quantification of diabetic macular edema. Arch Ophthalmol. 1987;105(2):218–22.
9. Klein M. Prevention and treatment of the complications of diabetes mellitus. N Engl J Med. 1995;333(12):802.
10. Aroca PR, Salvat M, Fernandez J, et al. Risk factors for diffuse and focal macular edema. J Diabetes Complications. 2004;18(4):211–5.
11. Gandorfer A. Diffuse diabetic macular edema: pathology and implications for surgery. Dev Ophthalmol. 2007;39:88–95.
12. Joussen AM, Murata T, Tsujikawa A, et al. Leukocyte-mediated endothelial cell injury and death in the diabetic retina. Am J Pathol. 2001;158(1):147–52.
13. Nishikiori N, Osanai M, Chiba H, et al. Glial cell-derived cytokines attenuate the breakdown of vascular integrity in diabetic retinopathy. Diabetes. 2007;56(5):1333–40.
14. Joussen AM, Poulaki V, Le ML, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. FASEB J. 2004;18(12):1450–2.
15. Lu M, Kuroki M, Amano S, et al. Advanced glycation end products increase retinal vascular endothelial growth factor expression. J Clin Invest. 1998;101(6):1219–24.
16. Blankenship GW. Diabetic macular edema and argon laser photocoagulation: a prospective randomized study. Ophthalmology. 1979;86(1):69–78.
17. Antcliff RJ, Spalton DJ, Stanford MR, et al. Intravitreal triamcinolone for uveitic cystoid macular edema: an optical coherence tomography study. Ophthalmology. 2001;108(4):765–72.
18. Murata T, Ishibashi T, Khalil A, et al. Vascular endothelial growth factor plays a role in hyperpermeability of diabetic retinal vessels. Ophthalmic Res. 1995;27(1):48–52.
19. Roberts WG, Palade GE. Increased microvascular permeability and endothelial fenestration induced by vascular endothelial growth factor. J Cell Sci. 1995;108(Pt 6):2369–79.
20. Lutty GA, McLeod DS, Merges C, et al. Localization of vascular endothelial growth factor in human retina and choroid. Arch Ophthalmol. 1996;114(8):971–7.

21. Gilbert RE, Vranes D, Berka JL, et al. Vascular endothelial growth factor and its receptors in control and diabetic rat eyes. Lab Invest. 1998;78(8):1017–27.
22. Adamis AP, Berman AJ. Immunological mechanisms in the pathogenesis of diabetic retinopathy. Semin Immunopathol. 2008;30(2):65–84.
23. Chung EJ, Roh MI, Kwon OW, et al. Effects of macular ischemia on the outcome of intravitreal bevacizumab therapy for diabetic macular edema. Retina. 2008;28(7):957–63.
24. Arevalo JF, Fromow-Guerra J, Sanchez JG, et al. Primary intravitreal bevacizumab for subfoveal choroidal neovascularization in age-related macular degeneration: results of the Pan-American Collaborative Retina Study Group at 12 months follow-up. Retina. 2008;28(10):1387–94.
25. Fang X, Sakaguchi H, Gomi F, et al. Efficacy and safety of one intravitreal injection of bevacizumab in diabetic macular oedema. Acta Ophthalmol. 2008;86(7):800–5.
26. Kook D, Wolf A, Kreutzer T, et al. Long-term effect of intravitreal bevacizumab (avastin) in patients with chronic diffuse diabetic macular edema. Retina. 2008;28(8):1053–60.
27. •• 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(8):972–9. *Randomized controlled trial showing bevacizumab superior to macular laser for the treatment of DME.*
28. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina. 2006;26(8):859–70.
29. •• Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789–801. *Randomized controlled trial showing ranibizumab superior to macular laser for the treatment of DME.*
30. •• Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117(6):1064–1077 e35. *Randomized controlled trial showing ranibizumab superior to triamcinolone or macular laser for the treatment of DME.*
31. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci USA. 2002;99(17):11393–8.
32. Rakic JM, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003;44(7):3186–93.
33. Gaudreault J, Fei D, Rusit J, et al. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci. 2005;46(2):726–33.
34. Do DV, Nguyen QD, Shah SM, et al. An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema. Br J Ophthalmol. 2009;93(2):144–9.
35. •• Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. Ophthalmology. 2011;118(9):1819–26. *Randomized controlled trial showing aflibercept superior to macular laser for the treatment of DME.*
36. • Martin DF, Maguire MG, Ying GS, et al., Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364(20):1897–908. *Randomized controlled trial showing no difference in visual outcome for patients treated with ranibizumab or bevacizumab for neovascular AMD.*
37. Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology. 2005;112(10):1747–57.