Intravitreal Aflibercept as Rescue Therapy for Post-Radiation Cystoid Macular Edema Resistant to Intravitreal Bevacizumab: Outcomes at 1 Year

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Keywords

Tumor · Choroidal melanoma · Radiotherapy · Cystoid macular edema · Anti-VEGF

Abstract

Background/Aims: To investigate the efficacy of intravitreal aflibercept as rescue therapy for post-radiation cystoid macular edema (CME) resistant to prior treatment with intravitreal bevacizumab (IVB). **Methods:** Retrospective, interventional, case-controlled series. Eyes with persistent post-radiation CME were treated with intravitreal aflibercept (2 mg/0.05 mL). Central macular thickness (CMT) and visual acuity were compared to a matched control group treated with only IVB at 1 year. **Results:** Ten eyes of 10 patients were included, with 5 eyes in the intervention and 5 in the control group. The eyes in the intervention group had previously been treated with IVB (mean 11.6 injections, range 6–22) but failed to show resolution of CME. Following rescue treatment with a mean of 9 injections of aflibercept, the mean CMT was reduced from 463 ± 138 to 267 ± 80 μm ($p = 0.02$) and the mean Snellen visual acuity was improved from 20/67 to 20/42 ($p = 0.03$). At 1 year, the eyes in the intervention group had lower CMT (267 ± 80 vs. 361 ± 71 μm , $p = 0.09$) and significantly better Snellen visual acuity (20/48 vs. 20/76, $p =$

0.02) compared to the control group. **Conclusions:** Aflibercept may be an effective rescue therapy for persistent post-radiation CME in eyes with incomplete response to IVB, with reduction in CMT and improvement in visual acuity.

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Introduction

Post-radiation cystoid macular edema (CME) is a common cause of vision loss following plaque radiotherapy for uveal melanoma [1, 2], occurring in up to 70% of eyes after iodine-125 plaque radiotherapy at 2 years [3]. Prior studies have identified many factors that are associated with the development of post-radiation CME including larger tumor size, higher radiation dose, and increased central macular thickness (CMT) at presentation [3, 4], which may help clinicians identify patients at higher risk.

As both uveal melanoma and ischemic sequelae of radiotherapy elevate levels of VEGF [5], intravitreal anti-VEGF agents have been commonly utilized for patients with post-radiation CME [6–8]. Multiple reports have noted improvement in visual acuity and CMT in eyes with post-radiation CME treated with intravitreal bevacizumab (IVB) [7, 9]; however, a subset of patients will de-

Table 1. Intravitreal aflibercept for postradiation cystoid macular edema resistant to intravitreal bevacizumab: baseline ocular and tumor features

Feature	Intervention group (<i>n</i> = 5 eyes)	Control group (<i>n</i> = 5 eyes)	<i>p</i> value
Age, years	62.6 (62, 57–69)	56 (58, 41–70)	0.40
Gender			
Female	5	4	
Male	0	1	
Race			
Caucasian	5	5	
Ocular features			
Choroidal melanoma	5	5	
Lens crystalline	5	5	
Epiretinal membrane	0	0	
Fluorescein angiography-evident cystoid macular edema	0	0	
Optical coherence tomography-evident cystoid macular edema	0	0	
logMAR visual acuity			
Affected eye	0.19 (0.18, 0.10–0.3)	0.15 (0, 0–0.60)	0.73
Central macular thickness, μ m			
Affected eye	315.2 (272, 252–489)	329 (283, 247–552)	0.53
Fellow eye	267 (255, 232–302)	266 (266, 248–281)	0.91
Tumor dimensions, mm			
Basal diameter	10.7 (10, 6–16)	10.9 (11, 7–18)	0.88
Thickness	3.6 (3.6, 2.2–4.7)	4.6 (3.9, 2.5–9.6)	0.58
Distance to foveola	4.3 (3, 0.5–12)	4.9 (2.5, 2–15)	0.89
Distance to optic nerve	5.4 (6, 3–9)	5 (5, 0.5–12)	0.90

Figures are numbers or means with medians and ranges in parentheses.

velop CME that is persistent despite a fixed-dose monthly therapy [7]. Rescue therapies for such patients with recalcitrant post-radiation CME have not been well described to date.

Aflibercept (Eylea; Regeneron Pharmaceuticals, Inc.) is a fully human, soluble recombinant VEGF receptor decoy that inhibits VEGF isoforms A and B (VEGF-A, VEGF-B) and placental growth factor (PlGF). Preclinical studies have shown that the binding affinity of aflibercept for VEGF-A is higher than native VEGF receptors [10]. The purpose of this study was to assess the efficacy of intravitreal aflibercept as rescue therapy for persistent post-radiation CME resistant to prior treatment with IVB.

Methods

Institutional Review Board approval from Wills Eye Hospital was obtained for this retrospective, interventional, case-controlled series. This research adhered to the tenets of the Declaration of

Helsinki and was conducted in accordance with regulations set forth by the Health Insurance Portability and Accountability Act. All patients were managed at the Ocular Oncology Service of Wills Eye Hospital, Philadelphia, PA, USA.

The clinical records of all patients with persistent post-radiation CME following iodine-125 plaque radiotherapy for uveal melanoma treated with intravitreal aflibercept were reviewed. Persistent post-radiation CME was defined as increased or stable CMT compared to baseline values despite a minimum of 3 monthly standard-dose (1.25 mg) IVB treatments. For the purpose of this study, change in CMT between baseline and follow-up was classified as decreased (>10% decrease in CMT compared to baseline), stable (within 10% of baseline CMT), or increased (>10% increase in CMT compared to baseline).

The following demographic and clinical features were recorded: age, gender, lens status, past ocular and medical history, Snellen visual acuity, tumor location, tumor diameter, and tumor thickness. Parameters of iodine-125 plaque radiotherapy, including total dose (cGy) and dose rate (cGy/h) to the tumor apex, base, optic disc, and foveola, were noted. Details regarding onset and treatment for post-radiation CME were also recorded.

Five eyes of 5 patients with persistent post-radiation CME were treated with aflibercept and included in the intervention group. All

Table 2. Intravitreal aflibercept for postradiation cystoid macular edema resistant to intravitreal bevacizumab: radiation parameters

Feature	Intervention group (<i>n</i> = 5 eyes)	Control group (<i>n</i> = 5 eyes)	<i>p</i> value
Radiation dose, cGy			
Tumor apex	7,200 (7,000, 7,000–8,000)	7,600 (8,000, 7,000–8,000)	0.37
Tumor base	14,254 (13,840, 11,350–20,440)	17,710 (16,460, 9840–24,200)	0.36
Foveola	6,158 (3,170, 1,581–13,001)	3,745 (3,949, 2,560–4,184)	0.39
Optic disc	2,584 (2,554, 1,548–3,647)	3,717 (3,910, 1,690–5,595)	0.20
Radiation rate, cGy/h			
Tumor apex	74.1 (74.7, 59.2–84.8)	76.7 (81.7, 60.2–85.9)	0.75
Tumor base	143.8 (147.6, 120.4–172.9)	175.6 (176.7, 103.8–223.9)	0.27
Foveola	65.5 (33.8, 13.4–138.0)	38.1 (42.4, 22.0–42.8)	0.38
Optic disc	26.6 (25.5, 16.5–38.7)	37.4 (33.6, 17.8–60.1)	0.30
Onset of optical coherence tomography-evident cystoid macula edema			
Months following plaque	22.8 (14, 8–43)	25.6 (16, 9–61)	0.73
logMAR visual acuity, affected eye	0.47 (0.48, 0.40–0.60)	0.60 (0.60, 0–0.88)	0.47
CMT, affected eye, μ m	463.4 (495, 354–642)	444.4 (427, 374–552)	0.66
CMT, fellow eye, μ m	267 (265, 256–293)	270 (264, 254–299)	0.81

Figures are means with medians and ranges in parentheses.

eyes were treated with a minimum of 6 monthly injections of intravitreal aflibercept, with follow-up examinations and spectral domain optical coherence tomography (OCT) performed every 4 weeks. After 6 months, the treatment interval could be adjusted based on clinical response. Outcomes at 6 months and 1 year were then compared with a matched control group comprised of 5 eyes of 5 patients with persistent post-radiation CME treated only with IVB. Controls were matched for baseline tumor features, CMT, visual acuity, the number of prior IVB treatments received, and follow-up interval.

Snellen visual acuities were converted to logMAR equivalents for statistical analysis. Using a Student *t* test analysis (GraphPad Software Inc., La Jolla, CA, USA), a *p* value <0.05 was considered statistically significant. The primary outcomes measured included change in CMT and visual acuity following treatment with aflibercept.

Results

Baseline features including patient age, gender, race, lens status, visual acuity, CMT in the affected and fellow eye, tumor thickness, tumor diameter, and tumor distance to the foveola were statistically similar between the intervention and control group (Table 1).

In the intervention group, mean logMAR visual acuity at the time of melanoma diagnosis was 0.19 ± 0.10 (Snellen 20/30). Mean tumor basal diameter was 10.7 mm (median 10, range 6–16) and mean tumor thickness was 3.6

mm (median 3.6, range 2.2–4.7). In the control group, mean logMAR visual acuity at the time of melanoma diagnosis was 0.15 ± 0.26 (Snellen 20/28). Mean tumor basal diameter was 10.9 mm (median 11, range 7–18) and mean tumor thickness was 4.6 mm (median 3.9, range 2.6–9.6). Angiographic or OCT-evident CME, macular ischemia, and epiretinal membrane were not present in any eye at baseline. All patients were phakic throughout the study period.

Details of iodine-125 plaque radiotherapy are summarized in Table 2. In the intervention group, OCT-evident post-radiation CME occurred at a mean of 23 months (median 14, range 8–43). Mean CMT at diagnosis of post-radiation CME was 479 ± 123 μ m and mean logMAR visual acuity was 0.47 ± 0.08 (Snellen 20/60) in the affected eye. In the control group, OCT-evident post-radiation CME occurred at a mean of 26 months (median 16, range 9–61). Mean CMT at diagnosis of post-radiation CME was 444 ± 71 μ m and mean logMAR visual acuity was 0.60 ± 0.39 (Snellen 20/79) in the affected eye.

Treatment outcomes are summarized in Table 3. In the intervention group, eyes were treated with a mean of 11.6 IVB injections (median 10, range 6–22) over a mean duration of 13 months (median 9, range 8–24). Following treatment with 6 monthly injections of intravitreal aflibercept, mean CMT improved from 463 ± 138 to 289

Table 3. Intravitreal aflibercept for postradiation cystoid macular edema resistant to intravitreal bevacizumab: treatment outcomes

Feature	Intervention group	Control group	Comparison between groups, <i>p</i> value
Prior cystoid macular edema treatment			
Total prior intravitreal bevacizumab injections	11.6 (10, 6–22)	11 (11, 11–11)	0.84
Treatment duration, months	13.2 (9, 8–24)	17.4 (12.4, 10.5–31)	0.41
Baseline at initiation of rescue therapy			
Central macular thickness, affected eye, μm	463.4 (407, 329–682)	406.8 (413, 288–568)	0.60
Central macular thickness, fellow eye, μm	262.6 (254, 221–293)	279.4 (275, 252–307)	0.44
logMAR visual acuity	0.53 (0.48, 0.40–0.70)	0.51 (0.40, 0.30–0.88)	0.73
Outcomes at 6 months			
Central macular thickness, affected eye, μm	288.8 (277, 204–393)	374.2 (331, 289–512)	0.09
<i>p</i> value	0.04	0.66	–
logMAR visual acuity	0.32 (0.30, 0.18–0.54)	0.58 (0.48, 0.30–1.0)	0.03
<i>p</i> value	0.03	0.20	–
Outcomes at 1 year			
Number of rescue therapy injections	9 (8, 8–11)	10 (10, 9–11)	
Central macular thickness, affected eye, μm	267.4 (268, 193–387)	361.2 (331, 282–457)	0.09
<i>p</i> value	0.02	0.49	–
logMAR visual acuity	0.32 (0.40, 0.0–0.54)	0.58 (0.54, 0.40–0.88)	0.02
<i>p</i> value	0.03	0.09	–

Figures are means with medians and ranges in parentheses.

$\pm 68 \mu\text{m}$ ($p = 0.04$) and mean logMAR visual acuity improved from 0.53 ± 0.15 (Snellen 20/67) to 0.32 ± 0.19 (Snellen 20/42, $p = 0.03$). A statistically significant reduction in CMT was observed following only 2 aflibercept injections ($p = 0.04$), with an illustrative case depicted in Figure 1. At the mean final follow-up of 12.8 months (range 12–14), logMAR visual acuity remained stable at 0.32 ± 0.23 (Snellen 20/42, $p = 0.03$) and CMT further improved to $267.4 \mu\text{m}$ ($p = 0.02$) following a mean of 10 (range 9–12) aflibercept injections. Following the 6-month time point, the treatment interval was extended in all patients to a mean of 8.6 weeks (range 6–13).

Compared to the control group, the eyes in the intervention group had comparatively lower CMT (289 ± 68 vs. $374 \pm 94 \mu\text{m}$, $p = 0.10$) and better visual acuity (0.32 ± 0.19 vs. 0.56 ± 0.28 , $p = 0.03$) at 6 months. These differences were maintained at 1 year, with lower CMT (289 ± 70 vs. $361 \pm 71 \mu\text{m}$, $p = 0.10$) and better visual acuity (0.38 ± 0.21 vs. 0.58 ± 0.18 , $p = 0.02$) in the intervention group. There were no injection-related complications.

Discussion

Plaque radiotherapy is the standard of care for most small or medium-sized choroidal melanomas, providing excellent local tumor control [11]. However, vision loss is common following plaque radiotherapy. In a series of 1,106 patients, Shields et al. [2] reported visual acuity outcomes of 20/200 or worse in up to 68% of patients treated with plaque radiotherapy for uveal melanoma at 10 years, with many of such outcomes attributed to sequelae of radiation retinopathy.

To better address visual acuity loss from CME specifically, recent work has sought to prevent occurrence of post-radiation CME as well as identify patients who may be at risk for CME development. Shah et al. [12] found that the use of IVB (1.25 mg) at 4-month intervals following plaque radiotherapy reduced the rate of OCT-evident CME (26 vs. 40%) and moderate vision loss (15 vs. 28%) in treated versus untreated eyes at 2 years, offering clinicians a possible preventative strategy. Moreover, a recent report identified that eyes with subclinical macular edema (greater than a 10- μm difference in CMT between the affected and fellow eye) at baseline were more

Fig. 1. Spectral domain optical coherence tomography of a 59-year-old female with post-iodine-125 plaque radiotherapy cystoid macular edema. While absent at diagnosis (**a**), cystoid macular edema developed 8 months following radiotherapy (**b**). After 10 intravitreal injections of bevacizumab (**c**), the edema persisted. Following treatment with aflibercept, the edema resolved as seen after 3 (**d**) and 5 (**e**) rescue treatments. CMT, central macular thickness; VA, visual acuity.

likely to develop CME after radiation ($p = 0.005$; hazard ratio 1.77), offering clinicians an OCT-based criterion to identify high-risk eyes [4].

Similarly, recent case series have sought to evaluate rescue therapies for persistent CME in eyes in which monthly anti-VEGF therapy fails to achieve CME resolution. Bui et al. [13] reported CMT and visual acuity outcomes in 2 patients with persistent post-radiation CME treated with the Ozurdex[®] dexamethasone implant (Allergan, Inc., Troy Hills, NJ, USA). The authors noted sustained anatomic improvement with Ozurdex[®] compared to prior IVB and intravitreal triamcinolone treatments, but visual acuity improved in only 1 of 2 eyes. Tarmann et al. [14] also reported outcomes in 4 eyes treated with Ozurdex[®] for persistent post-radiation CME despite prior IVB therapy. Similar to the results of Bui et al. [13], improvement in CMT was noted in all eyes but visual acuity improved in only 2 of 4 eyes. In addition, Finger and Chin [15] reported the efficacy of high-dose (2.0 mg) ranibizumab in treating 10 patients' persistent radiation retinopathy despite monthly, standard-dose ranibizumab, hypothesizing that a higher-dose anti-VEGF blockade may improve treatment response in patients with recalcitrant disease. The authors noted that while 80% of the eyes had a statistically significant improvement in CMT at 1 year, visual acuity remained stable.

The use of aflibercept for post-radiation CME is currently off-label. In this series, we found a statistically significant reduction in CMT ($p = 0.02$) and improvement in visual acuity ($p = 0.03$) following the use of monthly aflibercept at 6 months, gains that remained statistically significant at 1 year. In contrast, CMT did not improve significantly ($p = 0.49$) and visual acuity worsened ($p = 0.09$) in the control group at 1 year. Comparing groups, CMT was lower ($p = 0.09$) and visual acuity was significantly better ($p = 0.02$) in the aflibercept group at 1 year. Differing from the findings of Finger and Chin [15] evaluating high-dose ranibizumab therapy and the series evaluating Ozurdex[®] as rescue therapy for persistent post-radiation CME [13–15], statistically significant improvement in vision was observed with aflibercept treatment.

The precise mechanism for the observed reduction in CMT and improvement in visual acuity with aflibercept compared to IVB is speculative. Aflibercept has been demonstrated to bind VEGF-A with over 100-fold greater affinity than bevacizumab, possibly resulting in a more sustained VEGF-A inhibition [16–18]. Pharmacokinetic studies have also noted a longer predicted duration of action for aflibercept compared to bevacizumab and ranibizumab [19, 20]. In addition, aflibercept inhibits not only VEGF-A but additional growth factors including

VEGF-B and PlGF, which have been implicated in the pathogenesis of cystoid edema in other disease states including diabetic macular edema [16–18]. PlGF blockade may also have anti-inflammatory effects, as PlGF signaling has been implicated in monocyte chemotaxis and tissue factor (i.e., factor III, thromboplastin, CD142) production [21]. The higher affinity anti-VEGF blockade, longer duration of action, and simultaneous blockade of the PlGF cascade may all contribute to the visual acuity and CMT benefit noted with aflibercept in this series. Lastly, mechanisms of tachyphylaxis, including upregulation of VEGF receptors or metabolic changes altering pharmacokinetics of bevacizumab drug absorption, have been previously described with the use of anti-VEGF agents and could result in a dose-independent reduction in bevacizumab treatment response over time [22].

In the present study, exudative recurrences did not occur following treatment with aflibercept at a mean final follow-up of 12.8 months. In addition, all patients treated with aflibercept could be transitioned to a “treat and extend” regimen at 6 months, with treatment interval extension ranging from 6 to 13 weeks, potentially reducing treatment burden. Longer follow-up will be necessary to determine if the effect of aflibercept on CMT reduction and visual acuity reduction is maintained. A large cohort study has previously reported loss of at least 5 lines of Snellen visual acuity in up to 33% of patients undergoing plaque radiotherapy for uveal melanoma at 5 years [2]. Patients in the intervention group were followed for a mean of 45 months (3.7 years) from the time of plaque radiotherapy to the final follow-up. Over that time, mean logMAR visual acuity changed from 0.19 (Snellen 20/30) to 0.32 (Snellen 20/42), a loss of approximately 1 line of Snellen visual acuity. In the context of prior work noting significant visual loss following plaque radiotherapy in eyes with uveal melanoma, we believe the visual acuity results of this study are reflective of the improved outcomes that can be achieved after radiotherapy in the anti-VEGF era.

This study has several limitations, including the retrospective nature and the small sample size. In addition, while no statistically significant differences between the intervention and control group were present at baseline, exact matching of a control group was not possible. In addition, follow-up fluorescein angiography after initiation of rescue therapy was not available in all patients, and thus subsequent development of macular ischemia and potential influence on visual acuity outcomes could not be evaluated. However, given the rarity of choroidal melanoma and paucity of information regarding rescue ther-

apy for persistent CME, these results could be relevant and warrant future consideration. Additional studies, including the evaluation of aflibercept in treatment-naïve patients and prospective, randomized trials comparing treatment options would be necessary to clarify best practices.

In conclusion, intravitreal aflibercept was an effective rescue treatment for post-radiation CME in eyes with incomplete response to IVB. Statistically significant improvement in CMT and logMAR visual acuity was observed at 6 months that was maintained at 1-year. Additional follow-up and inclusion of a larger cohort is necessary to further define the role of aflibercept as rescue therapy for persistent post-radiation CME.

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Statement of Ethics

Institutional Review Board approval from Wills Eye Hospital was obtained for this study. This research adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with regulations set forth by the Health Insurance Portability and Accountability Act.

Disclosure Statement

The authors do not have any proprietary interests in the materials described in the report. No conflicting relationship exists for any author. Arman Mashayekhi, MD has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions

Design of the study: M.A.K., A.M., and C.L.S. Conduct of the study: M.A.K., A.M., C.L.S., and J.A.S. Data collection and analysis: M.A.K. and A.M. Interpretation of data: M.A.K., A.M., C.L.S., and J.A.S. Manuscript preparation: M.A.K., A.M., C.L.S., and J.A.S.

References

- 1 Horgan N, Shields CL, Mashayekhi A, et al: Classification and treatment of radiation maculopathy. *Curr Opin Ophthalmol* 2010; 21:233–238.
- 2 Shields CL, Shields JA, Cater J, et al: Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1,106 consecutive patients. *Arch Ophthalmol* 2000;118:1219–1228.
- 3 Horgan N, Shields CL, Mashayekhi A, et al: Early macular morphological changes following plaque radiotherapy for uveal melanoma. *Retina* 2008;28:263–273.
- 4 Mashayekhi A, Schönbach E, Shields CL, et al: Early subclinical macular edema in eyes with uveal melanoma: association with future cystoid macular edema. *Ophthalmology* 2015; 122:1023–1029.
- 5 Missotten GSO, Notting IC, Schlingemann RO, et al: Vascular endothelial growth factor a in eyes with uveal melanoma. *Arch Ophthalmol* 2006;124:1428–1434.
- 6 Finger PT, Chin KJ: Intravitreal ranibizumab (lucentis) for radiation maculopathy. *Arch Ophthalmol* 2010;128:249–252.
- 7 Mashayekhi A, Rojanaporn D, Al-Dahmash S, et al: Monthly intravitreal bevacizumab for macular edema after iodine-125 plaque radiotherapy of uveal melanoma. *Eur J Ophthalmol* 2014;24:228–234.
- 8 Gupta A, Muecke JS: Treatment of radiation maculopathy with intravitreal injection of bevacizumab (Avastin). *Retina* 2008;28:964–968.
- 9 Reichstein D: Current treatments and preventive strategies for radiation retinopathy. *Curr Opin Ophthalmol* 2015;26:157–166.
- 10 Holash J, Davis S, Papadopoulos N, et al: VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci USA* 2002; 99:11393–11398.
- 11 Jampol LM, Moy CS, Murray TG, et al: The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report No 19. *Ophthalmology* 2002;109:2197–2206.
- 12 Shah SU, Shields CL, Bianciotto CG, et al: Intravitreal bevacizumab at 4-month intervals for prevention of macular edema after plaque radiotherapy of uveal melanoma. *Ophthalmology* 2014;121:269–275.
- 13 Bui KM, Chow CC, Mieler WF: Treatment of recalcitrant radiation maculopathy using intravitreal dexamethasone (Ozurdex) implant. *Retin Cases Brief Rep* 2014;8:167–170.
- 14 Tarmann L, Langmann G, Mayer C, et al: Ozurdex® reduces the retinal thickness in radiation maculopathy refractory to bevacizumab. *Acta Ophthalmol* 2014;92:e694–e696.
- 15 Finger PT, Chin KJ: High-dose (2.0 mg) intravitreal ranibizumab for recalcitrant radiation retinopathy. *Eur J Ophthalmol* 2013;23:850–856.
- 16 Stewart MW, Rosenfeld PJ: Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol* 2008;92:667–668.
- 17 Stewart MW, Rosenfeld PJ, Penha FM, et al: Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina* 2012;32:434–457.
- 18 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;15:171–185.
- 19 Stewart MW, Rosenfeld PJ: Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol* 2008;92:667–668.
- 20 Stewart MW: Predicted biologic activity of intravitreal bevacizumab. *Retina* 2007;27:1196–1200.
- 21 Clauss M, Weich H, Breier G, et al: The vascular endothelial growth factor receptor Flt-1 mediates biological activities. Implications for a functional role of placenta growth factor in monocyte activation and chemotaxis. *J Biol Chem* 1996;271:17629–17634.
- 22 Gasperini JL, Fawzi AA, Khondkaryan A, et al: Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. *Br J Ophthalmol* 2012;96:14–20.