Graefes Arch Clin Exp Ophthalmol (2016) 254:1851–1856
DOI 10.1007/s00417-016-3426-7

INFLAMMATORY DISORDERS

A Large Outbreak of Fulminant Bacterial Endophthalmitis after Intravitreal Injection of Counterfeit Bevacizumab

Morteza Entezari[1] · Saeed Karimi[2] · Hamid Ahmadieh[3] · Amir Hossein Mahmoudi[4] · Hamid Parhizgar[4] · Mehdi Yaseri[5]

Received: 19 January 2016 / Revised: 21 April 2016 / Accepted: 22 June 2016 / Published online: 4 July 2016

Abstract
Purpose This study reports the findings in a large series of patients with acute bacterial endophthalmitis after intravitreal injection of bevacizumab (IVB) in two eye hospitals.
Methods Medical records were reviewed for patients who presented with acute fulminant endophthalmitis in one or two eyes following intravitreal injection of bevacizumab from two separate batches in two eye hospitals.
Results Twenty-eight eyes of 21 patients presented with acute endophthalmitis 12–48 hours after IVB injection. Cultures from the eyes and the vials were positive for *E. coli* and *Citrobacter*, each in one of the hospitals. All patients were initially treated with topical, intravitreal, and systemic antibiotics. Twenty-four eyes underwent pars plana vitrectomy. Best corrected visual acuity (BCVA) was 1.27 ± 0.89 logMAR before IVB injecti,on which decreased to 2.80 ± 0.45 LogMAR after presentation of endophthalmitis and 2.12 ± 0.97 logMAR three months after IVB injection. Final visual acuity was found to be no light perception in four eyes.
Conclusions This large outbreak of *E.coli* and *Citrobacter* endophthalmitis occurred after intravitreal injection of counterfeit bevacizumab. Visual outcomes were very poor.

Keywords Outbreak · Endophthalmitis · Bevacizumab

The work was carried out by Ophthalmic Research center Shahid Beheshti Medical University.

✉ Morteza Entezari
entmort@hotmail.com

[1] Ophthalmic Research Center, Department of Ophthalmology, Imam Hossein Medical Center, Shahid Beheshti Medical Sciences, Shahid Madani Ave., Tehran, Iran

[2] Ophthalmic Research Center, Department of Ophthalmology, Torfe Hospital, Shahid Beheshti Medical Sciences, Tehran, Iran

[3] Ophthalmic Research Center, Department of Ophthalmology, Labbafinejad Hospital, Shahid Beheshti Medical Sciences, Tehran, Iran

[4] Ophthalmic Research Center, Department of Ophthalmology, Razi Hospital, Tehran, Iran

[5] Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, USA) is a full-length humanized monoclonal antibody against vascular endothelial growth factor-A (VEGF-A) [1].

Despite being off-label for intraocular injection, bevacizumab has been extensively used in the treatment of vascular leakage and neovascular diseases such as age-related macular degeneration (AMD), retinal vein occlusion (RVO), proliferative diabetic retinopathy (PDR), and diabetic macular edema (DME) [2–4]. Since 2005, after Rosenfeld et al. published the results of their pilot study, intravitreal injection of bevacizumab has been one of the most widespread minor procedures in ophthalmology worldwide [5–8].

Bevacizumab is injected directly into the vitreous cavity and is generally well-tolerated with a low overall complication rate [9, 10]. Nevertheless, intravitreal injection of bevacizumab is not entirely free of adverse effects, most of which are related to the administration procedure than to the drug per se [11]. Endophthalmitis following intravitreal injection, a rare but feared complication, has been reported to have an incidence of 0.02–0.05 % [9, 10]. In published data from the Comparison of AMD Treatments Trials (CATT) study, six cases of endophthalmitis (0.05 %) were observed after 10,957

intravitreal injections of anti-VEGF drugs [12]. Sustained elevation of intraocular pressure (IOP) and severe intraocular inflammation have been increasingly reported following IVB injection [13–17]. Although the exact cause is yet to be determined, it is believed that mishandling of the drug during storage or repackaging as well as allergic reactions might be involved [13, 14, 18]. Recently, several outbreaks of bacterial and fungal infections, or sterile inflammations, have raised concern about the safety of the drug-preparation process [19–24]. Included among these was a report on a series of 12 cases of Streptococcus endophthalmitis after intravitreal injection of bevacizumab [20] and a large series of 80 cases of culture-negative endophthalmitis after intravitreal injection of counterfeit bevacizumab [24].

In the present case series, we report a large outbreak of acute-onset bacterial endophthalmitis following intravitreal injection of counterfeit bevacizumab, and will describe the clinical characteristics and outcomes of 28 cases of endophthalmitis at the same time period at two hospitals in Tehran in which the administered drug came from two different batches.

Methods

Twenty-eight eyes of 21 patients presented with acute-onset bacterial endophthalmitis following IVB injection between February 24 and February 26, 2015, in two eye hospitals simultaneously. Medical records and results of microbiologic evaluation of these cases were retrospectively reviewed. This study was approved by the institutional review board of the Ophthalmic Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

All injections were done using a sterile technique. In the first hospital, all injections were performed at the end of cataract procedures or vitrectomy from a previously unused single vial of bevacizumab. In the second hospital, all intravitreal injections were carried out in an operating room designated for intravitreal injections and again from a single, new vial. These two vials showed different batch numbers. Before the procedure, physicians scrubbed their hands and wore masks and sterile gloves. After cleaning the skin around the eye with a solution of povidone-iodine 10 % and instilling a single drop of povidone-iodine 5 % (Betadine; Alcon Laboratories, Inc., Fort Worth, TX, USA) in the cul-de-sac, a sterile lid speculum was placed. Topical proparacaine 0.5 % drops were used for local anesthesia. Prophylactic antibiotic eye drops were prescribed three times daily for 3 days post-injection.

The collected data included age, sex of each patient, the affected eye and its lens status, the date of the previous bevacizumab injection, the underlying diagnosis and the indication for IVB injection, and the pre-injection visual acuity. The presentation and diagnostic data for endophthalmitis were also recorded including the date of presentation, visual acuity and intraocular pressure, the presenting symptoms and signs, and the initial management as well as the microbiologic results. In addition, the clinical course of post-injection endophthalmitis was recorded, including visual acuity, routes of treatment with antibiotics and steroids, pars plana vitrectomy and other surgical interventions, as well as visual acuity and the status of the eye at the last follow-up examination.

To present the data, we used mean, standard deviation, frequency, and percent, with a 95 % confidence interval (95 % CI). To evaluate the change of best corrected visual acuity (BCVA) we used Wilcoxon's signed–rank test. All statistical analysis was performed by SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) P-values less than 0.05 were considered as statistically significant.

Results

In total, 28 eyes of 21 patients were included in this study. Among them, 11 (52.4 %) were male and 10 (47.6 %) were female. Fourteen right eyes (50 %) and 14 left eyes (50 %) were involved. Of 28 eyes, nine (32.1 %) were infected with *E. coli* in the first hospital, and 19 eyes (67.9 %) were infected by *Citrobacter* in the second hospital. *E. coli* was cultured from the same batch that was used in the first hospital. *Citrobacter* was cultured from the same batch that was used in the second hospital. The infected vials caused endophthalmitis in all treated patients. All patients were followed for 3 months (Table 1).

Symptoms and signs of a fulminant endophthalmitis was observed in nine eyes of eight patients after intravitreal injection of bevacizumab at the end of cataract or vitreous surgery in the operation room from a single batch in the first hospital, and 19 eyes of 13 patients from the other single batch in the second hospital within 12–48 (20.2 ± 9.7) hours following the IVB injection.

All patients were admitted with the diagnosis of endophthalmitis. Anterior chamber and vitreous tap was performed followed by intravitreal injection of vancomycin (1 mg) + ceftazidime (2.25 m g).Pars plana vitrectomy was performed on 24 (85.7 %) eyes. Topical steroid, fortified and systemic vancomycin, and ceftazidime were started for all patients; a systemic steroid was prescribed after 24 hours and continued for 10 days. Repeat vitrectomy and silicone oil injection was done for five eyes; in two of them it was performed in combination with penetrating keratoplasty due to severe keratitis. Conjunctival flap and amniotic membrane graft was performed in two other eyes for the prevention of corneal melting.

The mean BCVA was 1.27 ± 0.89 LogMAR before bevacizumab injection, 2.80 ± 0.45 LogMAR after presentation of endophtha,lmitis and 2.12 ± 0.97 LogMAR 3 months

Table 1 Specifications of all affected cases

Row	ID	Sex	Age	Eye	BCVA		Time (Hour)	Group	Vitx	Re vitx + silicone	Diagnostic
					Pre	Post	Final				
1	1	Male	87	OS	CF 1.5 m	LP	HM	19	E. coli	+	_	Cataract + CNV
2	2	Female	87	OS	CF 1 m	NLP	NLP	48	E. coli	-	_	Cataract + CNV
3	3	Male	54	OS	LP	LP	HM	18	E. coli	+silicone	_	Vitrectomy + PDR
4	4	Male	55	OS	3/10	LP	NLP	24	E. coli	+silicone	_	Cataract + BRVO
5	5	Female	33	OD	HM	HM	HM	24	E. coli	_	_	Vitrectomy + PDR
6	6	Female	72	OD	4/10	LP	NLP	36	E. coli	+silicone	_	DME
7	6			OS	1/10	NLP	NLP	36	E. coli	-	_	Cataract + BRVO
8	7	Male	73	OD	2/10	LP	LP	36	E. coli	+silicone	_	Cataract + BRVO
9	8	Female	67	OD	3/10	3/10	4/10	24	E. coli	-	_	Cataract + BRVO
10	9	Male	54	OS	2/10	HM	20/200	12	Citrobacter	+	_	DME
11	9			OD	1/10	HM	20/200	12	Citrobacter	+	_	DME
12	10	Female	60	OD	HM	LP	LP	12	Citrobacter	+	+silicone	DME + BRVO
13	11	Male	50	OS	3/10	LP	LP	12	Citrobacter	+	+silicone	DME
14	11			OD	2/10	LP	LP	12	Citrobacter	+	+silicone	DME
15	12	Male	34	OS	CF 1 m	LP	CF 1 m	12	Citrobacter	+		DME + BRVO
16	12	Male	28	OS	2/10	LP	CF 1 m	12	Citrobacter	+	+silicone	CSR
17	14	Female	59	OS	1/10	LP	CF 1 m	24	Citrobacter	+	+silicone	Vitreous Hemorrhage
18	14			OD	4/10	LP	LP	24	Citrobacter	+	_	Vitreous Hemorrhage
19	15	Male	61	OD	HM	LP	LP	24	Citrobacter	+silicone	_	DME + BRVO
20	16	Female	56	OD	2/10	HM	20/40	12	Citrobacter	+	_	BRVO
21	16			OS	3/10	HM	20/50	12	Citrobacter	+	_	BRVO
22	17	Male	63	OS	CF 1 m	LP	CF 1 m	12	Citrobacter	+silicone	_	BRVO
23	18	Male	71	OD	CF 1 m	LP	CF 1 m	12	Citrobacter	+silicone	_	CNV
24	19	Female	74	OD	HM	LP	HM	24	Citrobacter	+silicone	_	CNV
25	20	Female	61	OS	6/10	HM	1/10	24	Citrobacter	+silicone	_	DME
26	20			OD	6/10	LP	HM	24	Citrobacter	+silicone	_	DME
27	21	Female	51	OS	1/10	HM	20/100	12	Citrobacter	+	_	DME
28	21			OD	CF 1 m	HM	CF 1 m	12	Citrobacter	+	_	DME
Mean			59.5		1.27†		2.12	20.2			
SD			15.6		0.89		0.97	9.7			
P for change							0.002				

* Based on Wilcoxon's signed–rank test

† Based on logMAR, in this calculation a HM of 1 meter was considered to be equivalent to 2.8 logMAR, and LP and NLP were considered to be approximately 2.9 and 3.1 logMAR, respectively

CNV(choroidal neovascularization), PDR (proliferative diabetic retinopathy), DME (diabetic macular edema), BRVO (branch retinal vein occlusion), CSR (central serous retinopathy)

after intravitreal injections of bevacizumab. Final visual acuity was no light perception in four eyes. All eyes were saved without a need for enucleation or evisceration.

Discussion

The 3-month clinical outcomes in this largest outbreak of bacterial endophthalmitis following intravitreal injection of counterfeit bevacizumab have been poor. Only four patients (14.2 %) recovered useful vision (>1/10) in the affected eye. Previous studies have reported poor visual outcomes in post-intravitreal injection endophthalmitis, with 59–80 % of cases having hand-motions or worsened final visual acuity.[10–25] The outcomes in this case series are consistent with the results of prior published reports [10, 25].

Our patients developed the acute and fulminant form of post-IVB injection endophthalmitis. Mean time between intravitreal injections of bevacizumab and presentation of endophthalmitis was 20.2 hours (less than 24 hours), which is

unusual for an infectious endophthalmitis. The fulminant course of the disease and positive cultures in all cases and vials with severe endophthalmitis in all treated patients indicate a highly contaminated drug. Although there was no case of enucleation or evisceration in this outbreak, at three 3 months post-presentation, 16 eyes (57 %) had the visual acuity of hand-motions or worse. Final visual acuity was NLP in four (14.2 %) eyes and LP in six (21.4 %) eyes. The mean BCVA decreased significantly from 1.27 ± 0.89 LogMAR to 2.12 ± 0.97 LogMAR ($p = 0.002$) before and 3 months after intravitreal injections of bevacizumab, respectively. There were seven cases of bilateral endophthalmitis that were injected from a single batch. In bilateral cases, final visual acuity was NLP in both eyes of one patient and LP in both eyes of another patient, which was a disastrous outcome. All affected cases were treated with topical, intravitreal, and intravenous vancomycin and ceftazidime, but this treatment resulted in infection control only in four eyes (14.2 %); urgent PPV was required in 24 eyes (85.7 %) to control endophthalmitis (at post-IVB injection day 2). Despite reports about the effects of silicone oil as an antimicrobial or globe-salvaging agent, final visual outcomes in this outbreak, even in the silicone oil-filled eyes were poor [26–29].

Vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab and ranibizumab are frequently used in the treatment of neovascular age-related macular degeneration (AMD), as well as retinal vascular diseases, including retinal vein occlusion (RVO) and diabetic retinopathy [30-33]. Endophthalmitis after intravitreal injection of anti-VEGF agents is rare and occurs between 1 in 2,000 and 1 in 5,000 injections according to the previously reported studies. Half of the cases are culture-negative, while those that are culture-positive most commonly grow *Staphylococcus* and *Streptococcus* species [9, 10]. A published data from the CATT study showed that ranibizumab and bevacizumab have similar efficacy in the treatment of neovascular AMD with comparable rates of endophthalmitis after intravitreal injection of these two drugs [12]. Reusing the same bevacizumab vial for multiple injections seems not to increase its frequency in comparison to single-use ranibizumab vials. To date, other large series found no difference in the endophthalmitis risk in patients receiving bevacizumab as compared to ranibizumab [12, 34-38]. Bevacizumab is used as an "off-label" drug; in most countries it is prepared by compounding pharmacies for intravitreal use. The involvement of a compounding pharmacy introduces an additional step between the drug manufacturer and the treating physician, and this additional step may result in increased risk of contamination of the medication. Most of the previously reported culture-positive outbreaks occurred secondary to repackaging in compounding pharmacies [39-41]. The Pan-American Collaborative Retina Study Group (PACORES) reported more frequent endophthalmitis (6/1833 injections, 0.33 %) in eyes injected using previously compounded aliquots than in eyes given injections from the same multidose vial (1/2470 injections, 0.04 %) that was reused appropriately [42]. A series of 12 patients in Florida treated with bevacizumab from a single compounding pharmacy developed endophthalmitis with a common strain of *Streptococcus mitis/oralis* [20].

In our country, ophthalmologists do not employ compounding pharmacies as a source for individual doses of bevacizumab. Alternatively, they draw the dose directly from the bottle and use it for about 15–20 eyes. Bottles are obtained from the distributors, which in turn claim to buy the drug from the manufacturer. Since the process involves the drug changing hands twice, it is vulnerable to the introduction of the counterfeit drug. Unfortunately, these hospitals had bought two counterfeited bevacizumab vials from invalid distributors.

Counterfeit medicines are fake products that are deliberately and fraudulently manufactured to be mistaken for legitimate drugs. They may be contaminated or contain the wrong or inactive ingredient. They could also have the right active ingredient but at the wrong dose. Some counterfeit bottles contain not just water, but ethanol, citrate, and polyethylene glycol, which are added to the content to inhibit microbial growth [43]. Because the markup on counterfeit drugs is so high, they have become attractive to organized crime groups.

Bevacizumab is distributed as a 4- or 16-mL preservative-free single-use vial. Counterfeit bevacizumab poses a significant risk for ophthalmology and oncology patients. An outbreak of endophthalmitis following the counterfeit bevacizumab has previously been reported in China. Eighty out of 116 patients that received intravitreal injections from three vials of counterfeit bevacizumab developed culture-negative endophthalmitis, and the endotoxin was identified in the vitreous samples [24].

To our knowledge this report is the largest culture-positive outbreak of endophthalmitis after intravitreal injection of counterfeit bevacizumab. In the present case series, the first counterfeit batch was contaminated with E. coli and the second one was contaminated with Citrobacter. E. coli and Citrobacter are Gram-negative bacteria in the Enterobacteriaceae family. These bacteria can be found almost everywhere in contaminated soil, water, wastewater, etc.

There is no current consensus on the preferred treatment of post-injection endophthalmitis. The Endophthalmitis Vitrectomy Study did not enroll patients with post-injection endophthalmitis, so its findings cannot be directly applied to these patients. Topical, intravitreal, and systemic antibiotic therapy in mild cases and PPV with or without silicone oil injection in severe cases have been reported as treatment of post-injection endophthalmitis [44].

In summary, in this outbreak 28 eyes were affected by virulent strains of E. coli or Citrobacter after receiving an intravitreal injection of contaminated counterfeit bevacizumab at the same time at two separate hospitals in Tehran. This

outbreak, like in previously reported studies, confirmed that bilateral injections should be done from separate batches. According to the acute-onset course and poor outcomes of post-intravitreal injection endophthalmitis, we recommend prompt treatment with vitrectomy. Expensive drugs like bevacizumab are at risk of being replaced with counterfeit drugs, so vigilance is needed on the part of physicians, drug distributors, healthcare providers, and governments to prevent such a disastrous event in the future.

Compliance with ethical standards

Funding No funding was received for this research.

Conflict of Interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. For this type of study, formal consent is not required.

References

1. Velez-Montoya R, Oliver SC, Olson JL, Fine SL, Mandava N, Quiroz-Mercado H (2013) Current knowledge and trends in age-related macular degeneration: today's and future treatments. Retina 33:1487–1502
2. Bakri SJ, Larson TA, Edwards AO (2008) Intraocular inflammation following intravitreal injection of bevacizumab. Graefes Arch Clin Exp Ophthalmol 246:779–781
3. Velez-Montoya R, Oliver SC, Olson JL, Fine SL, Quiroz-Mercado H, Mandava N (2014) Current knowledge and trends in age-related macular degeneration: genetics, epidemiology, and prevention. Retina 34:423–441
4. Kimoto K, Kubota T (2012) Anti-VEGF agents for ocular angiogenesis and vascular permeability. J Ophthalmol 2012:852183
5. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS (2005) Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 112: 1035–1047
6. Rosenfeld PJ, Moshfeghi AA, Puliafito CA (2005) Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging 36:331–335
7. Ziemssen F, Sobolewska B (2011) Therapeutic efficacy of bevacizumab for age-related macular degeneration: what are the implications of CATT for routine management? Drugs Aging 28: 853–865
8. Jansen RM (2013) The off-label use of medication: the latest on the Avastin – Lucentis debacle. Med Law 32:65–77
9. McCannel CA (2011) Meta-analysis of endophthalmitis following intravitreal injection of anti-VEGF agents: causative organisms and possible prevention strategies. Retina 31:654–661
10. Moshfeghi AA, Rosenfeld PJ, Flynn HW Jr et al (2011) Endophthalmitis after intravitreal anti-vascular endothelial growth factor antagonists: a six-year experience at a university referral center. Retina 31:662–668
11. Yamashiro K, Tsujikawa A, Miyamoto K et al (2010) Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch. Retina 30:485–490
12. The CATT Research Group (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 364:1897–1908
13. Liu L, Ammar DA, Ross LA, Mandava N, Kahook MY, Carpenter JF (2011) Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: effects of long-term storage and product mishandling. Invest Ophthalmol Vis Sci 52: 1023–1034
14. Fielden M, Nelson B, Kherani A (2011) Acute intraocular inflammation following intravitreal injection of bevacizumab – a large cluster of cases. Acta Ophthalmol 89:e664–e665
15. Good TJ, Kimura AE, Mandava N, Kahook MY (2011) Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. Br J Ophthalmol 95:1111–1114
16. Yeh S, Albini TA, Moshfeghi AA, Nussenblatt RB (2012) Uveitis, the comparison of age-related macular degeneration treatments trials (CATT), and intravitreal biologics for ocular inflammation. Am J Ophthalmol 154:429–435
17. Damasceno N, Horowitz S, Damasceno E (2012) Anterior uveitis after treatment of age-related macular degeneration with ranibizumab and bevacizumab: uncommon complication. Clin Ophthalmol 6:1201–1205
18. Marticorena J, Romano V, Gómez-Ulla F (2012) Sterile endophthalmitis after intravitreal injections. Mediat Inflamm 2012:928123
19. Sheyman AT, Cohen BZ, Friedman AH, Ackert JM (2013) An outbreak of fungal endophthamitis after intravitreal injection of compounded combined bevacizumab and triamcinolone. JAMA Ophthalmol 131:864–869
20. Goldberg RA, Flynn HW Jr, Miller D, Gonzalez S, Isom RF (2013) Streptococcus endophthalmitis outbreak after intravitreal injection of bevacizumab: 1-year outcomes and investigative results. Ophthalmology 120:1448–1453
21. Yamashiro K, Tsujikawa A, Miyamoto K et al (2010) Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch. Retina 30:485–490
22. Khan P, Khan L, Mondal P (2013) Cluster endophthalmitis following multiple intravitreal bevacizumab injections from a single use vial. Indian J Ophthalmol
23. Entezari M, Ramezani A, Ahmadieh H, Ghasemi H (2014) Batch-related sterile endophthalmitis following intravitreal injection of bevacizumab. Indian J Ophthalmol 62:468–471
24. Wang F, Yu S, Liu K, Chen FE, Song Z, Zhang X, Xu X, Sun X (2013) Acute intraocular inflammation caused by endotoxin after intravitreal injection of counterfeit bevacizumab in Shanghai, China. Ophthalmology 120:355–360
25. Miller JM, Scott IU, Flynn HW Jr et al (2004) Endophthalmitis caused by Streptococcus pneumoniae. Am J Ophthalmol 138: 231–236
26. Chan CC, Holland EJ, Sawyer WI, Neff KD, Petersen MR, Riemann CD (2011) Boston type 1 keratoprosthesis combined with silicone oil for treatment of hypotony in prephthisical eyes. Cornea 30:1105–1109
27. Alexandridis E (1990) Silicone oil tamponade in the management of severe hemorrhagic detachment of the choroid and ciliary body after surgical trauma. Ophthalmologica 200:189–193
28. Skorpik C, Menapace R, Gnad HD, Paroussis P (1989) Silicone oil implantation in penetrating injuries complicated by PVR. Results from 1982 to 1986. Retina 9:8–14
29. Ozdamar A, Aras C, Ozturk R, Akin E, Karacorlu M, Ercikan C (1999) In vitro antimicrobial activity of silicone oil against endophthalmitis-causing agents. Retina 19:122–126

30. Abu-Yaghi NE, Bakri SJ (2012) The use of antivascular endothelial growth factor agents in the perioperative period in diabetic vitrectomy. Middle East Afr J ophthalmol 19:83–87
31. Sun X, Xu X, Zhang X (2011) Counterfeit bevacizumab and endophthalmitis. N Engl J Med 365:378–379
32. Fintak DR, Shah GK, Blinder KJ et al (2008) Incidence of endophthalmitis related to intravitreal injection of bevacizumab and ranibizumab. Retina 28:1395–1399
33. Mezad-Koursh D, Goldstein M, Heilwail G, Zayit-Soudry S, Loewenstein A, Barak A (2010) Clinical characteristics of endophthalmitis after an injection of intravitreal antivascular endothelial growth factor. Retina 30:1051–1057
34. Diago T, McCannel CA, Bakri SJ, Pulido JS, Edwards AO, Pach JM (2009) Infectious endophthalmitis after intravitreal injection of antiangiogenic agents. Retina 29:601–605
35. Pilli S, Kotsolis A, Spaide RF et al (2008) Endophthalmitis associated with intravitreal anti-vascular endothelial growth factor therapy injections in an office setting. Am J Ophthalmol 145:879–882
36. Cavalcante LL, Cavalcante ML, Murray TG et al (2010) Intravitreal injection analysis at the Bascom palmer eye institute: evaluation of clinical indications for the treatment and incidence rates of endophthalmitis. Clin Ophthalmol 4:519–524
37. Cheng J-W, Wei R-L (2011) Ranibizumab for age-related macular degeneration. N Engl J Med 364:582
38. Lee SH, Woo SJ, Park KH et al (2010) Serratia marcescens endophthalmitis associated with intravitreal injections of bevacizumab. Eye 24:226–232
39. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H et al (2008) Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 246:81–87
40. Garcia-Aguirre G, Vanzinni-Zago V, Quiroz-Mercado H (2013) Growth of Scytalidium sp. In a counterfeit bevacizumab bottle. Indian J Ophthalmol 61:523–525
41. Results of the Endophthalmitis Vitrectomy Study (1995) A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Endophthalmitis Vitrectomy Study Group. Arch Ophthalmol 113:1479–1496
42. Stewart MW (2013) Critical appraisal of ranibizumab in the treatment of diabetic macular edema. Clin Ophthalmol 7:1257–1267
43. Huang P, Niu W, Ni Z, Wang R, Sun X (2013) A meta-analysis of anti-vascular endothelial growth factor remedy for macular edema secondary to central retinal vein occlusion. PLoS One 8:e82454
44. Tan MH, McAllister IL, Gillies ME et al (2014) Randomized controlled trial of intravitreal ranibizumab versus standard grid laser for macular edema following branch retinal vein occlusion. Am J Ophthalmol 157:237–247