Arch Biol Sci. 2022;74(1):49-55 https://doi.org/10.2298/ABS220116003Z

Impact of the COVID-19 pandemic on patients receiving intravitreal injections

Ningzhi Zhang, Xuejun He, Yiqiao Xing and Ning Yang*

Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan, China

***Corresponding author**: rootyangning@whu.edu.cn

Received: January 16, 2022; **Revised**: January 19, 2022; **Accepted**: January 20, 2022; **Published online**: February 2, 2022

Abstract: We analyzed the economic benefits versus safety risks of sharing anti-vascular endothelial growth factor (VEGF) vials during the coronavirus disease (COVID-19) pandemic. This single-center retrospective study analyzed the data of patients with neovascular age-related macular degeneration (nAMD), proliferative diabetic retinopathy (PDR) and retinal vein occlusion (RVO) who received anti-VEGF between January 2016 and July 2021 at Renmin Hospital, Wuhan University, China. Costs were compared of the two protocols of intravitreal injections (IVIs) of ranibizumab, aflibercept and conbercept after (i) splitting the vial content for use in two patients and after (ii) disposal of the remaining vial content after use in a single patient, with the COVID-19 outbreak considered as the demarcation point. The incidence rates of post-injection endophthalmitis (PIE) pre- and post-outbreak were analyzed. The mean cost of a single IVI increased by 33.3%, from 3917.67±71.69 to 5222.67±84.98 Chinese Yuan during the pandemic. The incidences of IVI-related culture-positive PIE were 0.0134% (3 in 22448) and 0.0223% (1 in 4479), respectively, before and after the pandemic (P=0.6532). We conclude that vial sharing of IVIs in a large clinical institution is not associated with increased PIE risk and can significantly reduce the cost of therapy.

Keywords: anti-vascular endothelial growth factor; COVID-19; intravitreal injection; post-injection endophthalmitis; vial splitting

Abbreviations: vascular endothelial growth factor (VEGF); intravitreal injection (IVI); neovascular age-related macular degeneration (nAMD); proliferative diabetic retinopathy (PDR); post-injection endophthalmitis (PIE); retinal vein occlusion (RVO)

INTRODUCTION

Vascular endothelial growth factor (VEGF) plays a critical role in the pathogenesis and progression of many angiogenic diseases, such as cancer, endometriosis, osteoarthritis and chronic kidney disease [1-5]. It is at the center of the process of retinal and choroidal neovascularization, including age-related macular degeneration, retinopathy of prematurity and proliferative diabetic retinopathy [6,7]. After decades of studies, anti-VEGF drugs are now applied in clinical practice to treat retinal diseases, such as diabetic macular edema, proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO) and neovascular age-related macular degeneration (nAMD), which are the leading causes of blindness worldwide [8-13]. In China, the overall prevalence of diabetes was 11.2%, according to a study conducted between 2015 and 2017 [14]. The number of people with any type of AMD was around 12.01 million in China in 1990 and increased to 26.65 million by 2015. This study also pointed out that the predicted number of patients with AMD would reach 55.19 million by 2050 [15].

Currently in China, three antiangiogenic agents are commonly available for the treatment of retinal vascular diseases: ranibizumab (Lucentis®, Novartis, Basel, Switzerland), aflibercept (Eylia®; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) and conbercept (Lumitin®; Chengdu Kanghong Pharmaceuticals Group Co., Ltd., Chengdu, China) [16-18].

Chinese society and family structure have continuously changed over recent decades due to the rapidly

growing number of people aged over 60 years, which now (2021) accounts for nearly 18.70% of the total Chinese population. Along with the growing trend of aging societies, higher incidence rates of senile retinal vascular diseases have led to greater demands for anti-VEGF medicines in China [19]. The increasingly widespread application of intravitreal anti-VEGF therapy for retinal diseases has had revolutionary effects in enhancing patients' vision. However, it has significantly impacted public health and financial stress due to its high retail price and the requirement for multiple injections. A single intravitreal injection (IVI) of anti-VEGF costs more than 5000 CNY, while the per capita disposable income of Chinese residents was 32189 CNY in 2020. Thus, the expense of multiple injections undoubtedly exerts a heavy financial burden on both family and public health institutions. The prices of three types of anti-VEGF medications were downregulated in China from approximately 5600 to 4000 CNY as of January 1, 2020. This price adjustment was thought to be good news for patients.

After the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, the conventional practice of splitting the same vial between two syringes to inject into two separate eyes is no longer used. Instead, a vial is to be used for only one patient and the excess content of the vial is discarded. This approach to IVI was instituted to meet anti-epidemic requirements to avoid possible nosocomial infections caused by virus transmission. Theoretically, this may also reduce the incidence rates of injection-related adverse effects, such as post-injection endophthalmitis (PIE), which can lead to severe impairment of the patients' visual functions. Nevertheless, it causes significantly more financial stress on both patients and the National Public Health System.

The security and economic benefit of splitting vials into prefilled syringes or repackaging the remaining medication for IVIs has been extensively studied by foreign groups [20-22]. These strategies showed a favorable application prospect. However, the feasibility and necessity of extensive application of splitting anti-VEGF drugs for IVI has not been analyzed and discussed in China. In this study, we sought to weigh the advantages and disadvantages of vial sharing based on China's national conditions and the background of the COVID-19 pandemic. We evaluated the change in costs per eye treated with intravitreal ranibizumab, aflibercept or conbercept before and after the occurrence of the COVID-19 pandemic and determined the costs if the former rule were to be reapplied. Additionally, we investigated whether the incidence of PIE was closely associated with the procedure of splitting vials.

MATERIALS AND METHODS

Study design and subjects

This single-center, retrospective study was performed at the Department of Ophthalmology at Renmin Hospital of Wuhan University, which is the largest eye center in the Central China district. The study protocol was reviewed and was granted an exemption from requiring ethics approval by the Ethics Committee of Renmin Hospital of Wuhan University. It was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all the study participants.

Data were searched for all patients with nAMD, PDR or RVO who received intravitreal injections of anti-VEGF agents between January 2016 and July 2021. All patients involved had undergone a standardized diagnosis process, strict indication control and specialized therapy. Patients were assigned to two different groups to reflect the different rules for anti-VEGF IVI.

A diagnosis of endophthalmitis at Renmin Hospital of Wuhan University is clinically made on the basis of a typical medical history and ophthalmic examination, and a vitreous biopsy or a pars plana vitrectomy for microbiological analysis are routinely performed to assist diagnosis. To decrease possible errors that could have caused endophthalmitis related to a procedure other than an IVI into the study, patients who had undergone intraocular surgery after their last IVI were excluded. Moreover, patients diagnosed with uveitis who did not receive endophthalmitis treatment (intravitreal antibiotics with or without vitrectomy) within 1 week were considered probable sterile endophthalmitis cases, and also excluded.

Study procedure

Before December 2019, vials of ranibizumab, aflibercept and conbercept were split into two syringes to

provide IVI to two eyes (two patients). However, because of the new IVI rules after the outbreak of COVID-19 in Wuhan, anti-VEGF vials were no longer split, but a single dose was administered from a vial and the rest of the liquid was discarded.

We summarized the statistics of all patients who received IVIs of anti-VEGF agents. We also recorded the cases of injection-related PIE, including patient information, types of diseases, clinical treatment and culture results during two different periods: from January 2016 to December 2019 and from April 2020 to July 2021. The main outcomes were the mean costs in CNY of the single-IVI process for the three anti-VEGF agents (ranibizumab, aflibercept and conbercept) before and after stopping the practice of splitting vials to treat two patients, as well as the expected expenses if the former practice were to be reinstated. In addition, we evaluated PIE rates in these two different time-periods.

Statistical analysis

All statistical analyses were performed using the SPSS v26.0 software (IBM Inc., Armonk, NY, USA). Average costs are presented as mean ± standard deviation (SD). Descriptive statistics, including relative risk with 95% confidence intervals (CI), were used to compare the incidence rates of IVI-related PIE across the two time-periods. Categorical variables were compared using the chi-square test. Statistical significance was set at $P<0.05$.

RESULTS

The total number of intravitreal anti-VEGF injections from January 2016 to July 2021 was 26927. There were 22448 procedures (83.3%) before the COVID-19 outbreak in Wuhan (from January 2016 to December 2019) and 4479 procedures (16.7%) after lockdown was lifted in Wuhan (from April 2020 to July 2021). The mean cost of IVI of ranibizumab, aflibercept and conbercept was 3917.67±71.69 CNY before the pandemic, which increased to 5222.67±84.98 CNY after the pandemic (Table 1). Comparison of the costs associated with the two different rules revealed an increase of 33.3%. The expected cost for conducting IVI in the original manner would reduce the price to 3189.33±42.49 CNY (Table 2), indicating a 38.9% reduction from the current price and a 18.6% reduction from the original cost before the retail prices were lowered.

Before the pandemic, the IVI-related PIE incidence was 0.0134% (95% CI, 0.0028-0.0391%). After the pandemic, this incidence was 0.0223% (95% CI,

Table 1. Costs of intravitreal injection of anti-vascular endothelial growth factor drugs before and after pandemic outbreak.

Date	Drug	Cost of a vial (CNY)	Cost for one patient (CNY)	Preoperative examination (CNY)	Surgery-related cost (CNY)	Total cost (CNY)	Mean cost ± SD (CNY)	Number of cases of procedures
January 2016 to December 2019	Ranibizumab	5700	2850	338	738	3926	3917.67 ± 71.69	18139
	Aflibercept	5850	2925	338	738	4001		2106
	Conbercept	5500	2750	338	738	3826		2203
April 2020 to July 2021	Ranibizumab	3950	3950	418	738	5106	5222.67 ± 84.98	1531
	Aflibercept	4100	4100	418	738	5256		1497
	Conbercept	4150	4150	418	738	5306		1451

CNY, Chinese Yuan; SD, standard deviation

Table. 2. Expected cost using the original method with intravitreal injection of anti-vascular growth factor drugs.

Drug	Cost of a vial (CNY)	Cost for one patient (CNY)	Preoperative examination (CNY)	Surgery-related cost (CNY)	Total cost (CNY)	Mean cost ± SD (CNY)	Reduction proportion (compared with the costs)	
							Before the pandemic	After the pandemic
Ranibizumab	3950	1975	418	738	3131	3189.33 ± 42.49	18.6%	38.9%
Aflibercept	4100	2050	418	738	3206			
Conbercept	4150	2075	418	738	3231			

CNY, Chinese Yuan; SD, standard deviation

Table 3. Incidence of post-injection endophthalmitis (PIE) before and after the pandemic outbreak.

Date	Injections	Detailed Information of Recorded Cases						PIE Incidence (95%CI)
		Case	Age	Sex	Diagnosis	Drug	Treatment	
January 2016 to December 2019	22448	1	67	F	nAMD	R	PPV	0.0134% (0.0028–0.0391%)
		2	59	M	PDR	A	PPV	
		3	75	M	nAMD	R	PPV	
April 2020 to July 2021	4479	1	69	F	nAMD	C	PPV	0.0223% (0.0006–0.1243%)

A, aflibercept; C, conbercept; CI, confidence interval; F, female; M, male; nAMD, neovascular age-related macular degeneration; PDR, proliferative diabetic retinopathy; PIE, post-injection endophthalmitis; PPV, pars plana vitrectomy; R, ranibizumab

0.0006-0.1243%) (Table 3). All PIE cases considered in this study were culture-positive. By setting the operation of splitting anti-VEGF drug vials as a risk factor, we determined that the relative risk for developing PIE following the two different IVI rules was 1.6708 (0.1738-16.0656%). There was no significant difference between morbidity and risk of PIE related to the kinds of IVI approaches (chi-square test, P=0.6532).

Four PIE cases were identified (incidence 0.0149%; 95% CI 0.0041-0.0380%). The PIE cases occurred sporadically. In total, among the 19670 injections of ranibizumab, there were two PIE cases (incidence 0.0102%; 95% CI 0.0012-0.0367%). Among the 3603 injections of aflibercept, there was one case of PIE (incidence 0.0278%; 95% CI 0.0007-0.1545%). Among the 3654 injections of conbercept, there was one PIE case (incidence 0.0274%; 95% CI 0.0007-0.1524%). There was no statistically significant difference in the incidence rates among the three groups (chi-square test, P=0.5828).

Of the four PIE cases, the indication for anti-VEGF therapy was nAMD in three patients and PDR in one patient (Table 3). All the preceding procedures of IVIs adhered to the standard procedure, and patient-related risk factors for PIE were not identified.

DISCUSSION

We calculated and analyzed the financial influence of anti-VEGF IVI policies in China before and after the outbreak of COVID-19. With the decrease in retail prices of anti-VEGF medications, the average cost of a single injection of anti-VEGF to one eye increased by approximately 33.3% after COVID-19. Based on the average income of the Chinese population, this is a significant burden for patients. When we calculated the mean expected cost of these injections when following the former IVI protocol, we found that the estimated cost of each procedure with the vial-splitting approach would be reduced to about 3200 CNY, which amounts to 61.1% of the current procedure costs.

From January 2016 to December 2020, we conventionally split every vial of the anti-VEGF into two syringes to inject two separate patients, one after another, by IVI. Unlike Blom et al. [21], we did not implement pharmaceutical compounding because we only split ranibizumab, aflibercept and conbercept vials. After the outbreak of COVID-19 in Wuhan, new pandemic prevention rules resulted in many changes. COVID-19 is thought to be transmitted through aerosols, which poses a challenge for preventing and controlling nosocomial infections [23,24]. Since April 2020, in the Department of Ophthalmology at Renmin Hospital of Wuhan University, we no longer split the vials of any anti-VEGF agents for epidemic prevention. Once the vial is opened, it can only be used by one patient and the remaining liquid is discarded. This results in significant increase in the cost of a single injection. The epidemic has already had a marked impact on the medical financial budget in the short-term, and the new rule imposes a further burden on costs for both the individual and for public health resources. Moreover, we found that the rate of PIE was similar using either the pre-COVID-19 or post-COVID-19 IVI policies, indicating that vial-spitting procedures are safe, and at least will not increase the PIE rate.

Anti-VEGF drugs are expensive and require repeated injections to maintain their therapeutic effects [25]. Usually, patients who have indications for this therapy require more than one injection. In some

cases, more than 20 injections are needed. The degree of financial burden is directly related to patient adherence, particularly for low-income families [26], and patients with financial stress may reject therapy before completing the treatment course. In addition, patients who need to pay higher costs are more likely to feel anxious and annoyed when the therapeutic effects are unsatisfactory. They tend to consider that higher prices correspond to better results. This strong emotional reaction of patients is a fuse for doctor-patient conflicts. Therefore, it is necessary to take measures to reduce the cost of anti-VEGF therapy to ease the economic and psychological burden on patients. A previous study showed that bevacizumab vial sharing led to a reduction in public health-care costs [27]. Our results also demonstrated that vial sharing of other anti-VEGF agents in IVIs also reduced the costs for both patients and public health care.

With the outbreak of the COVID-19 pandemic, the insufficient storage and low buffer capacity of public health resources were exposed in China. The surging consumption of disposable medical resources has added a financial burden to society. Adjusting IVI rules to ease medical burdens, improve patient compliance and improve doctor-patient relationships requires attention. To maximize the use of leftover medication, some studies have investigated the feasibility and safety of repackaging the leftover intravitreal anti-VEGF agent to reduce the waste of public resources and patients' expenses [20]. In addition, another study provided a novel compounding method that split anti-VEGF biologics from single vials into multiple prefilled silicone oil-free syringes to improve the synthesis and storage of compounding drugs [28]. The authors found that drug stability and activity were not affected during the process of repackaging and storage. Some observations indicated that the splitting of vials into prefilled syringes is not dangerous [21]. The procedure may even decrease the rate of culture-positive PIE [22]. These strategies could indicate a possible direction for improving the public health-care system and further reducing of the financial burden.

Infectious endophthalmitis is the most visually damaging complication of IVI [29]. Most cases of endophthalmitis are exogenous and appear as complications of eye surgery or penetrating ocular trauma [30]. The number of these cases related to IVI of anti-VEGF medications has increased in recent years [31]. Theoretically, even in strict compliance with the standard sterile operations, the additional operation of splitting vials, or the increasing time interval of temporary storage between extraction of drugs and IVI may elevate the risk of contamination, which can lead to an increase in the incidence of injection-related endophthalmitis. In this study, we investigated whether the new rule contributed to a decrease in the incidence of PIE. We found that all PIE cases occurred sporadically. In all PIE cases, the preceding injection had adhered to the standard procedure, and no patients had known risk factors for PIE. In addition, neither deviation from the standard injection protocol nor patient-specific circumstances seem to have biased the results. The morbidity and risk of PIE did not change significantly when we split one vial into two syringes, indicating that such procedures are safe, and at least will not lead to higher rates of PIE. Analysis of the four PIE patients showed that the rates of PIE did not vary among the three different anti-VEGF agents investigated in our study. This conclusion was supported by other studies [32-34]. This evidence adds reliability to our comparison of the prevalence of PIE before and after the outbreak of COVID-19, without considering different types of anti-VEGF drugs.

Our study had some limitations. Owing to the relatively short research duration, the sample size of the included patients was relatively small. The sample size should be expanded by continuous accumulation of cases because the incidence of PIE was quite low (fewer than 0.25 per 1000 injections in this study). Furthermore, a previous study suggested that female and male patients differ in their proclivity for endophthalmitis after IVI of anti-VEGF agents, with women having higher odds of PIE [35]. Another report revealed that diabetes-related eye injuries and nAMD appear to be associated with higher PIE rates than RVO [36]. In addition, in terms of safety, we mainly focused on PIE, one of the most severe complications.

CONCLUSIONS

Essentially, every rule has two sides. It is necessary to find a balance between the advantages and disadvantages of each approach, and to attempt to pursue the maximum economic welfare of patients under the

premise of ensuring safety by adjusting rules flexibly according to various medical situations and social backgrounds. In this study, we found that the new IVI regulation imposed after the outbreak of COVID-19 in Wuhan significantly increased the financial burden on all patients; however, the incidence of PIE was not significantly associated with changes in the IVI rules. Thus, our study adds to the evidence that the splitting of vials into syringes for IVIs is safe and economical. We suggest that, with increasing vaccine coverage and with control over the pandemic, the vial-splitting protocol should be resumed. Strengthening the awareness of medical staff of strict sterility measures and improving professional and standardized procedures are important prerequisites for reinstating the original IVI rules. We will continue to complete post-epidemic data statistics to verify our results. In addition, we will investigate the stability, safety, sterility and efficacy of pharmaceutical compounding procedures in the near future.

Funding: The authors received no specific funding for this work.

Acknowledgments: We thank Ms. Wenye Cao for her kind suggestions.

Author contribution: NY conceived the idea and collected the clinical data for the study. NZ and XH analyzed the data and drafted the first version of the manuscript. NY and YX helped to optimize the protocol design, as well as to revise and edit the manuscript. All authors listed read the final version of the manuscript and approved it for publication.

Conflict of interest disclosure: The authors declare no conflict of interest.

Data availability: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov. 2016;15(6):385-403. https://doi.org/10.1038/nrd.2015.17
2. Chen L, Lin G, Chen K, Liang R, Wan F, Zhang C, Tian G, Zhu X. VEGF promotes migration and invasion by regulating EMT and MMPs in nasopharyngeal carcinoma. J Cancer. 2020;11(24):7291-301. https://doi.org/10.7150/jca.46429
3. Lavoz C, Alique M, Rodrigues-Diez R, Pato J, Keri G, Mezzano S, Egido J, Ruiz-Ortega M. Gremlin regulates renal inflammation via the vascular endothelial growth factor receptor 2 pathway. J Pathol. 2015;236(4):407-20. https://doi.org/10.1002/path.4537
4. Li W, Hsiao K, Wang C, Chang N, Hsu P, Sun C, Wu S, Wu M, Tsai S. Extracellular vesicle-associated VEGF-C promotes lymphangiogenesis and immune cells infiltration in endometriosis. Proc Natl Acad Sci U S A. 2020;117(41):25859-68. https://doi.org/10.1073/pnas.1920037117
5. Chen Y, Zhao B, Zhu Y, Zhao H, Ma C. HIF-1-VEGF-Notch mediates angiogenesis in temporomandibular joint osteoarthritis. Am J Transl Res. 2019;11(5):2969-82.
6. Wang H, Ramshekar A, Kunz E, Sacks DB, Hartnett ME. IQGAP1 causes choroidal neovascularization by sustaining VEGFR2-mediated Rac1 activation. Angiogenesis. 2020;23(4):685-98. https://doi.org/10.1007/s10456-020-09740-y
7. Ling S, Yang S, Hu X, Yin D, Dai Y, Qian X, Wang D, Pan X, Hong J, Sun X, Yang H, Paludan S, Cai Y. Lentiviral delivery of co-packaged Cas9 mRNA and a Vegfa-targeting guide RNA prevents wet age-related macular degeneration in mice. Nat Biomed Eng. 2021;5(2):144-56. https://doi.org/10.1038/s41551-020-00656-y
8. Ng D, Fung N, Yip F, Lai T. Ranibizumab for myopic choroidal neovascularization. Expert Opin Biol Ther. 2020;20(12):1385-93. https://doi.org/10.1080/14712598.2021.1830969
9. Lim L, Mitchell P, Seddon J, Holz F, Wong T. Age-related macular degeneration. Lancet. 2012;379(9827):1728-38. https://doi.org/10.1016/S0140-6736(12)60282-7
10. Wells J, Glassman A, Ayala A, Jampol L, Bressler N, Bressler S, Brucker A, Ferris F, Hampton G, Jhaveri C, Melia M, Beck R. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016;123(6):1351-9. https://doi.org/10.1016/j.ophtha.2016.02.022
11. Wong T, Cheung C, Larsen M, Sharma S, Simó R. Diabetic retinopathy. Nat Rev Dis Primers. 2016;2:16012. https://doi.org/10.1038/nrdp.2016.12
12. Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R, Gandorfer A, Ulbig M, Kampik A. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina. 2006 Nov;26(9):999-1005. https://doi.org/10.1097/01.iae.0000247165.38655.bf
13. Mitry D, Bunce C, Charteris D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database Syst Rev. 2013;(1):Cd009510. https://doi.org/10.1002/14651858.CD009510.pub2
14. Li Y, Teng D, Shi X, Qin G, Qin Y, Quan H, Shi B, Sun H, Ba J, Chen B, Du J, He L, Lai X, Li Y, Chi H, Liao E, Liu C, Liu L, Tang X, Tong N, Wang G, Zhang J, Wang Y, Xue Y, Yan L, Yang J, Yang L, Yao Y, Ye Z, Zhang Q, Zhang L, Zhu J, Zhu M, Ning G, Mu Y, Zhao J, Teng W, Shan Z. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. BMJ. 2020;369:m997. https://doi.org/10.1136/bmj.m997

15. Song P, Du Y, Chan KY, Theodoratou E, Rudan I. The national and subnational prevalence and burden of age-related macular degeneration in China. J Glob Health. 2017;7(2):020703. https://doi.org/10.7189/jogh.07.020703
16. Feng J, Qian J, Jiang Y, Zhao M, Liang J, Yin H, Chen Y, Yu W, Li X. Efficacy of Primary Intravitreal Ranibizumab for Retinopathy of Prematurity in China. Ophthalmology. 2017;124(3):408-9. https://doi.org/10.1016/j.ophtha.2016.10.032
17. Cai S, Yang Q, Li X, Zhang Y. The efficacy and safety of aflibercept and conbercept in diabetic macular edema. Drug Des Devel Ther. 2018;12:3471-83. https://doi.org/10.2147/DDDT.S177192
18. Liu K, Song Y, Xu G, Ye J, Wu Z, Liu X, Dong X, Zhang M, Xing Y, Zhu S, Chen X, Shen Y, Huang H, Yu L, Ke Z, Rosenfeld P, Kaiser P, Ying G, Sun X, Xu X. Conbercept for Treatment of Neovascular Age-related Macular Degeneration: Results of the Randomized Phase 3 PHOENIX Study. Am J Ophthalmol. 2019;197:156-67. https://doi.org/10.1016/j.ajo.2018.08.026
19. Xu T, Wang B, Liu H, Wang H, Yin P, Dong W, Li J, Wang Y, Yusufu M, Briant P, Reinig N, Ashbaugh C, Adelson J, Vos T, Bourne R, Wang N, Zhou M. Prevalence and causes of vision loss in China from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Lancet Public Health. 2020;5(12):e682-e91. https://doi.org/10.1016/S2468-2667(20)30254-1
20. Sodré S, Barbosa I, Pacheco I, Ferreira F, David M, Nascimento M, Arieta C, Vasconcellos J. Costs and benefits of bevacizumab vial sharing for the treatment of retinal diseases. BMC Public Health. 2019;19(1):1252. https://doi.org/10.1186/s12889-019-7562-y
21. Blom K, Bragadóttir R, Sivertsen M, Moe M, Jørstad Ø. Does Pharmaceutical Compounding of Vascular Endothelial Growth Factor Inhibitors for Intravitreal Use Alter the Risk of Post-injection Endophthalmitis? Ocul Immunol Inflamm. 2020;1-4. https://doi.org/10.1080/09273948.2020.1820530
22. Storey P, Tauqeer Z, Yonekawa Y, Todorich B, Wolfe J, Shah S, Shah A, Koto T, Abbey A, Morizane Y, Sharma P, Wood E, Morizane-Hosokawa M, Pendri P, Pancholy M, Harkey S, Jeng-Miller K, Obeid A, Borkar D, Chen E, Williams P, Okada A, Inoue M, Shiraga F, Hirakata A, Shah C, Prenner J, Garg S. The Impact of Prefilled Syringes on Endophthalmitis Following Intravitreal Injection of Ranibizumab. Am J Ophthalmol. 2019;199:200-8. https://doi.org/10.1016/j.ajo.2018.11.023
23. Du Q, Zhang D, Hu W, Li X, Xia Q, Wen T, Jia H. Nosocomial infection of COVID-19: A new challenge for healthcare professionals (Review). Int J Mol Med. 2021;47(4):31. https://doi.org/10.3892/ijmm.2021.4864
24. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res. 2020;188:109819. https://doi.org/10.1016/j.envres.2020.109819
25. Sodré S, Barbosa I, Pacheco I, Ferreira F, David M, Nascimento M, Arieta C, Vasconcellos J. Costs and benefits of bevacizumab vial sharing for the treatment of retinal diseases. BMC Public Health. 2019;19(1):1252. https://doi.org/10.1186/s12889-019-7562-y
26. Sivertsen M, Jørstad Ø, Grevys A, Foss S, Moe M, Andersen J. Pharmaceutical compounding of aflibercept in prefilled syringes does not affect structural integrity, stability or VEGF and Fc binding properties. Sci Rep. 2018;8(1):2101. https://doi.org/10.1038/s41598-018-20525-8
27. Gomi F, Toyoda R, Yoon A, Imai K. Factors of Anti-Vascular Endothelial Growth Factor Therapy Withdrawal in Patients with Neovascular Age-Related Macular Degeneration: Implications for Improving Patient Adherence. J Clin Med. 2021;10(14):3106. https://doi.org/10.3390/jcm10143106
28. Lode H, Gjølberg T, Foss S, Sivertsen M, Brustugun J, Andersson Y, Jørstad Ø, Moe M, Andersen J. A new method for pharmaceutical compounding and storage of anti-VEGF biologics for intravitreal use in silicone oil-free prefilled plastic syringes. Sci Rep. 2019;9(1):18021. https://doi.org/10.1038/s41598-019-54226-7
29. Sassalos T, Paulus Y. Prefilled syringes for intravitreal drug delivery. Clin Ophthalmol. 2019; 13: 701-6. https://doi.org/10.2147/OPTH.S169044
30. Durand M. Bacterial and Fungal Endophthalmitis. Clin Microbiol Rev. 2017;30(3):597-613. https://doi.org/10.1128/CMR.00113-16
31. Durand M. Endophthalmitis. Clin Microbiol Infect. 2013;19(3):227-34. https://doi.org/10.1111/1469-0691.12118
32. Borkar D, Obeid A, Su D, Storey P, Gao X, Regillo C, Kaiser R, Garg S, Hsu J. Endophthalmitis Rates after Bilateral Same-Day Intravitreal Anti-Vascular Endothelial Growth Factor Injections. Am J Ophthalmol. 2018;194:1-6. https://doi.org/10.1016/j.ajo.2018.06.022
33. VanderBeek B, Bonaffini S, Ma L. Association of compounded bevacizumab with postinjection endophthalmitis. JAMA Ophthalmol. 2015;133(10):1159-64. https://doi.org/10.1001/jamaophthalmol.2015.2556
34. Stem M, Rao P, Lee I, Woodward M, Faia L, Wolfe J, Capone A, Covert D, Dass A, Drenser K, Garretson B, Hassan T, Margherio A, Oh K, Raephaelian P, Randhawa S, Sneed S, Trese M, Yedavally S, William G, Ruby A. Predictors of Endophthalmitis after Intravitreal Injection: A Multivariable Analysis Based on Injection Protocol and Povidone Iodine Strength. Ophthalmol Retina. 2019;3(1):3-7. https://doi.org/10.1016/j.oret.2018.09.013
35. Bavinger J, Yu Y, VanderBeek B. Comparative risk of endophthalmitis after intravitreal injection with bevacizumab, aflibercept, and ranibizumab. Retina. 2019;39(10):2004-11. https://doi.org/10.1097/IAE.0000000000002351
36. Rayess N, Rahimy E, Shah C, Wolfe J, Chen E, DeCroos F, Storey P, Garg S, Hsu J. Incidence and clinical features of post-injection endophthalmitis according to diagnosis. Br J Ophthalmol. 2016;100(8):1058-61. https://doi.org/10.1136/bjophthalmol-2015-307707