DOI: 10.4274/tjo.galenos.2021.37075
Turk J Ophthalmol 2022;52:179-185

Original Article

Survey of Intravitreal Injection Preferences for the Treatment of Age-Related Macular Degeneration and Macular Edema Among Members of the Turkish Ophthalmological Association

V. Levent Karabaş*, Ecem Önder Tokuç**, Figen Şermet***

*Kocaeli University Faculty of Medicine, Department of Ophthalmology, Kocaeli, Turkey
**University of Health Sciences Turkey, Derince Training and Research Hospital, Clinic of Ophthalmology, Kocaeli, Turkey
***Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

Objectives: To analyze the current preferences of ophthalmologists for the treatment of macular edema and age-related macular degeneration (AMD) and to evaluate off-label use of bevacizumab in Turkey.

Materials and Methods: All members of the Turkish Ophthalmological Association were contacted by e-mail to complete an anonymous, 47-question internet-based survey. The second part of the survey (questions 36-47) was evaluated.

Results: When current legal regulations were considered, ophthalmologists used bevacizumab as the first-line agent in patients with diabetic macular edema (DME), AMD, and retinal vein occlusion (RVO) (58.25%, 55.89%, and 52.29%, respectively). When economic and legal constraints were disregarded, the participants' preference for bevacizumab in the treatment of DME, AMD, and RVO decreased (11.64%, 10.58%, and 10.93%, respectively). Approximately three-quarters (75.75%) of ophthalmologists stated that dispensing multiple syringes from a single bevacizumab bottle could increase the risk of endophthalmitis. Most participants (93.68%) did not feel legally safe from harm caused by off-label bevacizumab use. However, 66.43% of ophthalmologists stated that bevacizumab is as effective as other anti-vascular endothelial growth factor (anti-VEGF) drugs.

Conclusion: Bevacizumab is widely used as a first-line treatment for all indications of anti-VEGF use in the current reimbursement conditions, which preclude the right of ophthalmologists to treat according to their own preferences.

Keywords: Anti-VEGF, bevacizumab, aflibercept, ranibizumab, off-label, diabetic macular edema, age-related macular degeneration, retinal vein occlusion

Address for Correspondence: V. Levent Karabaş, Kocaeli University Faculty of Medicine, Department of Ophthalmology, Kocaeli, Turkey
E-mail: karabas@superonline.com **ORCID-ID:** orcid.org/0000-0001-7860-4603
Received: 16.04.2021 **Accepted:** 17.08.2021

Cite this article as: Karabaş VL, Önder Tokuç E, Şermet F. Survey of Intravitreal Injection Preferences for the Treatment of Age-Related Macular Degeneration and Macular Edema Among Members of the Turkish Ophthalmological Association. Turk J Ophthalmol 2022;52:179-185

Introduction

The treatment of neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO) is evolving as new research results become available. Ophthalmologists widely use intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents such as ranibizumab, aflibercept, and bevacizumab in the treatment of these conditions.[1,2,3,4] Aflibercept and ranibizumab were approved by the United States Food and Drug Administration (FDA) for the treatment of AMD, RVO, and DME. However, bevacizumab does not have FDA approval for ophthalmic use and is thus "off-label," despite being widely used.[5] Bevacizumab is also not approved for ophthalmologic use in Turkey. The ophthalmic off-label use of bevacizumab has caused great controversy due to the ethical, legal, economic, and political issues surrounding its use.[6]

As a global health issue, the substantial cost variation, the risk of endophthalmitis, the legal restriction of off-label use, the cost of obtaining medications, and reimbursements contribute to a controversial health policy and an ethical dilemma in regard to anti-VEGF agents. In Turkey, reimbursement regulations suggest three consecutive monthly injections of bevacizumab for the treatment of DME, AMD, and RVO. The aim of this study was to describe the preferences of ophthalmologists regarding anti-VEGF drugs and evaluate the off-label use of bevacizumab.

Materials and Methods

All members of the Turkish Ophthalmological Association were contacted via e-mail in May 2020 to complete a 47-question online survey conducted using SurveyMonkey (www.surveymonkey.com; SurveyMonkey, San Mateo, CA). Three reminder e-mails were sent to participants who had not completed the survey yet. Data collection was concluded on June 4, 2020. Results from the first part of the survey (questions 1-35) evaluating intravitreal injection techniques were published previously.[7] The second part of the survey (questions 36-47) evaluated ophthalmologists' approaches to bevacizumab and other FDA-approved anti-VEGF drugs for patients with DME, AMD, and RVO. The participants were divided into subgroups as representatives of private hospitals, private offices, public hospitals, city hospitals, university hospitals, training and research hospitals, and foundation universities. The research protocol was approved by the Institutional Ethics Committee and Review Board of Kocaeli University (number: KAEK 2020/219).

Results

In total, 892 ophthalmologists answered the questionnaire, and 660 participants who were actively performing intravitreal injections were included in the study. The institutions of the participants are presented in Table 1.

Considering the current reimbursement restrictions, 58.3% (332/570) of the participants used bevacizumab as a first-line agent in patients with DME (Figure 1). The participants' preference for bevacizumab varied between institutions (Table 2). Participants working in private offices were more likely to use aflibercept than bevacizumab (51.9%, 14/27 vs. 22.2%, 6/27).

Of the participants, 49.4% stated that they would prefer aflibercept as a first-line agent in patients with DME if there were no economic and reimbursement restrictions (Figure 2). Preferences for aflibercept were similar among institutions except in public hospitals (Table 3). Participants working in public hospitals preferred ranibizumab for patients with DME (43.8%, 21/48).

Considering the current reimbursement restrictions, over half of the participants (55.9%, 318/569) used bevacizumab as a first-line agent in patients with AMD (Figure 3). Bevacizumab was used in most institutions (Table 4). However, participants from private offices and foundation universities reported greater use of aflibercept for patients with AMD (51.9%, 14/27 and 59.4%, 19/32, respectively).

Most of the participants (61.7%, 350/567) stated that they would prefer aflibercept as first-line treatment for AMD if there were no economic and reimbursement restrictions (Figure 4).

Table 1. Demographics of the participants

Institutions	Number*	Percent
Private hospital	219/890	24.61
Private office	42/890	4.72
Public hospital	147/890	16.52
City hospital	48/890	5.39
University hospital	239/890	26.85
Training and research hospital	194/890	21.80
Foundation university	46/890	5.17

*Participants could choose more than one option

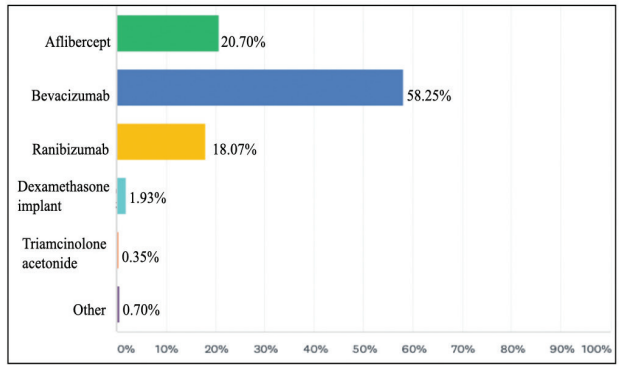

Figure 1. Ophthalmologists' preferences for anti-vascular endothelial growth factors and other agents in patients with diabetic macular edema under the current reimbursement restrictions

Under these circumstances, aflibercept was preferred for patients with AMD in all institutions (Table 5).

Over half the participants (52.3%, 297/568) used bevacizumab initially for patients with RVO under the current reimbursement restrictions. Participants in city hospitals (73.1%, 19/26), university hospitals (53.1%, 94/177), training and research hospitals (61.8%, 81/131), and private hospitals (53.2%, 84/158) mostly used bevacizumab, while the participants at foundation universities (31.3%, 10/32) and private offices (37.0%, 10/27) used aflibercept. However, participants in public hospitals preferred ranibizumab.

Overall, 35.5% of participants would prefer aflibercept as first-line therapy in patients with RVO if there were no economic and reimbursement restrictions. Participants in private hospitals (44.9%, 71/158), private offices (40.7%, 11/27), foundation universities (43.8%, 14/32), and training and research hospitals (38.9%, 51/131) mostly preferred aflibercept as a first-line agent. Participants in public hospitals mostly preferred ranibizumab (40.4%, 19/47), while dexamethasone implants were preferred as first-line treatment by those in city hospitals (53.9%, 14/26) and university hospitals (33.0%, 58/176).

Table 2. Preference for bevacizumab in patients with diabetic macular edema under the current reimbursement restrictions

Institutions	Number	Percent
Private hospital	90/159	56.60
Private office	6/27	22.22
Public hospital	22/48	45.83
City hospital	20/27	74.07
University hospital	103/178	57.87
Training and research hospital	91/131	69.47
Foundation university	13/32	40.63

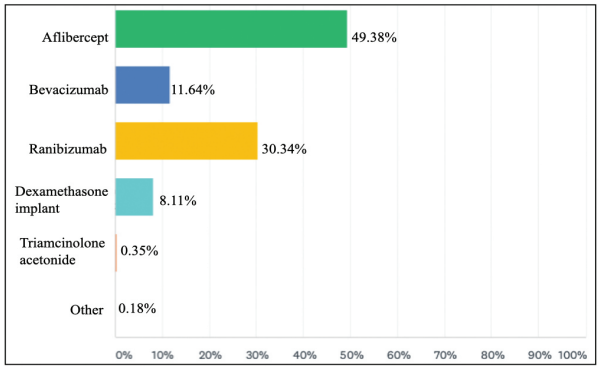

Figure 2. Ophthalmologists' preferences for anti-vascular endothelial growth factors and other agents in patients with diabetic macular edema if there were no economic and reimbursement restrictions

Table 3. Preference for aflibercept in patients with diabetic macular edema if there were no economic and reimbursement restrictions

Institutions	Number	Percent
Private hospital	**80/158**	**50.63**
Private office	17/27	62.96
Public hospital	14/48	29.17
City hospital	16/27	59.26
University hospital	82/176	46.59
Training and research hospital	73/131	55.73
Foundation university	17/31	54.84

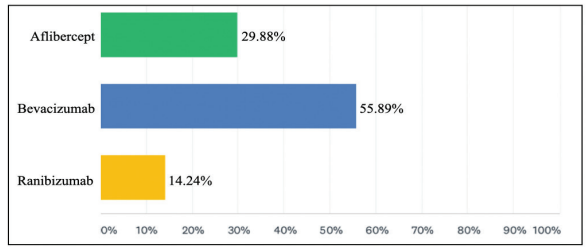

Figure 3. Ophthalmologists' use of anti-vascular endothelial growth factor agents in patients with age-related macular degeneration under the current reimbursement restrictions

Table 4. Preference for bevacizumab in patients with age-related macular degeneration under the current reimbursement restrictions

Institutions	Number	Percent
Private hospital	87/158	55.06
Private office	7/27	25.93
Public hospital	21/48	43.75
City hospital	19/27	70.37
University hospital	93/177	52.54
Training and research hospital	92/131	70.23
Foundation university	9/32	28.13

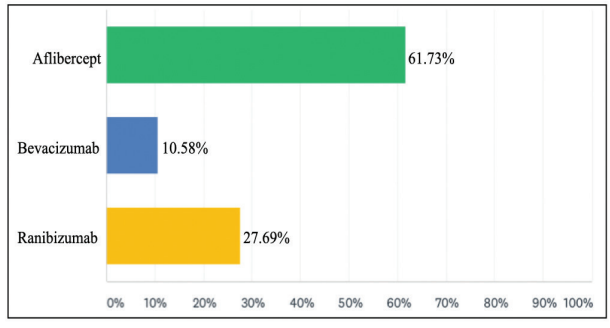

Figure 4. Ophthalmologists' preferences for anti-vascular endothelial growth factor agents in patients with age-related macular degeneration if there were no economic and reimbursement restrictions

Most of the participants (75.8%, 431/569) stated that dispensing multiple syringes from a single bevacizumab bottle could increase the risk of endophthalmitis (private hospitals: 59.5% [94/158]; private offices: 73.1% [19/26], public hospitals: 80.9% [38/47], city hospitals: 80.8% [21/26], university hospitals: 81.5% [145/178], training and research hospitals: 84.1% [111/132], and foundation universities: 78.1% [25/32]). However, 47.1% of the participants reported that they dispense multiple syringes from a single bevacizumab bottle (Table 6).

In addition, less than half (48.2%) of the participants stated that they did not feel under pressure to use a single bevacizumab bottle for more than one patient. The percentages of participants who felt pressure to use a single bevacizumab bottle on several patients are presented in Table 7. Unlike participants in other institutions, those in training and research hospitals were under greater pressure to use a single bevacizumab bottle for more than one patient (47.7%, 63/132). However, 16.2% of the participants did not use bevacizumab.

Some participants (25.6%) noted that they did not use bevacizumab while an approved anti-VEGF drug was available for that indication. Most of the participants (93.7%, 534/570) stated that they did not feel legally safe from harm caused by off-label bevacizumab use.

Overall, 66.4% (376/566) of participants stated that bevacizumab is as effective as other anti-VEGF drugs. In contrast, 60.6% of the participants stated that they think aflibercept is more effective and safer than other anti-VEGF agents (bevacizumab and ranibizumab) in patients with AMD, RVO, and DME (Table 8). However, participants in public hospitals stated that they think ranibizumab is more effective and safer than other anti-VEGFs (38.3%, 18/47).

Table 5. Preference for aflibercept in patients with age-related macular degeneration if there were no economic and reimbursement restrictions

Institutions	Number	Percent
Private hospital	95/157	60.51
Private office	16/27	59.26
Public hospital	23/48	47.92
City hospital	18/27	66.67
University hospital	100/176	56.82
Training and research hospital	90/131	68.70
Foundation university	26/32	81.25

Table 6. Participants who dispense multiple syringes from a single bevacizumab bottle

Institutions	Number	Percent
Private hospital	90/157	57.32
Private office	6/27	22.22
Public hospital	23/47	48.94
City hospital	8/26	30.77
University hospital	72/177	40.68
Training and research hospital	66/130	50.77
Foundation university	11/32	34.38

Discussion

Due to the necessity of using bevacizumab for the first three loading doses under the current reimbursement restrictions in our country, most ophthalmologists prefer bevacizumab as first-line therapy in patients with DME, RVO, and AMD. However, when reimbursement restrictions were not considered, ophthalmologists' drug preferences differed. Many participants working in private offices and foundation universities did not prefer bevacizumab as first-line therapy.

Diabetic Macular Edema

In Turkey, ophthalmologists utilize anti-VEGF injections as first-line therapy to treat DME. Due to the current reimbursement restrictions, 58.3% of ophthalmologists stated that they use bevacizumab as a first-line therapy in DME. However, participants working in private offices preferred aflibercept (51.9%). This may be related to the better socioeconomic level of the patients who receive service from private offices and the higher compliance of ophthalmologists with their drug preference. Nearly half (49.8%) of all the participants would prefer aflibercept if there was no reimbursement limitation.

Table 7. Participants who feel pressure to use a single bevacizumab bottle for several patients

Institutions	Number	Percent
Private hospital	36/156	23.08
Private office	3/27	11.11
Public hospital	18/47	38.30
City hospital	11/26	42.31
University hospital	73/178	41.01
Training and research hospital	63/132	47.73
Foundation university	7/32	21.88

Table 8. Participants who consider aflibercept more effective and safer in patients with age-related macular degeneration, retinal vein occlusion, and diabetic macular edema than other anti-vascular endothelial growth factor agents (bevacizumab and ranibizumab)

Institutions	Number	Percent
Private hospital	106/157	67.52
Private office	15/25	60.00
Public hospital	19/47	40.43
City hospital	17/26	65.38
University hospital	94/175	57.71
Training and research hospital	84/132	63.63
Foundation university	24/31	77.42

In the 2019 American Society of Retina Specialists (ASRS) global trends survey, most of the participants (Africa/Middle East: 74.0%; Asia/Pacific: 33.7%; and United States: 65.8%) used bevacizumab for initial treatment of DME based on the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T 2-year results.[8] However, in the same survey, European participants (39.8%) and Central and South American participants (33.6%) preferred aflibercept for patients with DME. The use of off-label drugs, cost effectiveness, and changing reimbursement policies of states may be the reasons for this difference. In the United States, 65.8% of ASRS participants preferred bevacizumab as a first-line agent for patients with DME. However, in the 2020 ASRS global trends survey, 57.8% of retina specialists in the United States chose aflibercept (pre-filled syringe [PFS]) for their own center-involving DME.[9] Similarly, in Europe, the preference of aflibercept increased from 39.8% for patients with DME in 2019 to 47.6%+20.7% (PFS+vial) for retina specialists' own center-involving DME in 2020.

In addition, 49.4% of the ophthalmologists in our study preferred aflibercept for the treatment of DME when reimbursement restrictions are not considered. This may be due to the doctors' desire to reduce the treatment burden (number of injections) with aflibercept. However, unlike in other institutions, participants in public hospitals (43.8%) preferred ranibizumab for the treatment of DME. The higher preference for ranibizumab may be due to the use of PFSs to reduce the risk of endophthalmitis. The use of a PFS eliminates most of the steps in injection preparation (aseptic), thereby reducing the risk of contamination.[10,11] The participants in public hospitals may prefer to use PFSs due to the lack of equipment and the lack of retina specialists to manage endophthalmitis complications that may occur after intravitreal injection.

Age-related Macular Degeneration

Anti-VEGF therapy is the current treatment for AMD. Under current reimbursement policies, bevacizumab was preferred for AMD treatment in all institutions except private offices and foundation universities. When restrictions were not considered, 61.7% of the participants stated that they would use aflibercept as the first-line therapy for AMD. In the 2020 ASRS global trends survey, 60.6% of American retina specialists stated that aflibercept delivers the most effective fluid resolution in wet AMD.[9] The participants may have thought that aflibercept is more effective for the treatment of standard AMD patients. The eight-week dosing regimen of aflibercept represents reduced treatment requirements in comparison with monthly dosing regimens and thus has the potential to reduce the treatment burden and risks associated with frequent injections.

In European countries, the usage of off-label bevacizumab for the treatment of AMD and associated cost vary from country to country.[12] The intravitreal administration of bevacizumab has also been a matter of legal dispute in European countries. Moreover, the specific factors influencing medication choice appear to go beyond clinical considerations. The controversy over the ophthalmic off-label use of bevacizumab remains remarkably unresolved within the world's largest single market. In the United States, 70.2% of American retina specialists use bevacizumab as the first-line anti-VEGF.[13]

Retinal Vein Occlusion

In this survey, no consensus among ophthalmologists was observed for the treatment of RVO when economic and reimbursement restrictions were ignored. According to the 2019 Euretina RVO guideline, intravitreal anti-VEGF therapy has become the standard of care for treating this disease.[14] According to the guideline, corticosteroids are important in the armamentarium of drugs for treating patients with RVO, but largely as a second choice. In the 2015 ASRS global trends survey, retina specialists primarily used anti-VEGF agents for the treatment of RVO.[15]

Use of Bevacizumab

Of the total participants, 93.7% stated that they did not feel that it was legally safe to use off-label bevacizumab. The legal safety of off-label bevacizumab use is also unclear in European countries.[12] Considering the current reimbursement restrictions in Turkey, it can be understood why the participants do not feel that it is safe. According to the Off-Label Drug Use guideline, "In our country, off-label drug use is not allowed for diseases that can be treated with medication within an approved indication. However, if there are treatment options that provide significant advantages according to scientific data, the request for off-label drug use is evaluated by the Institution."[16] However, the requirement of three doses of bevacizumab for reimbursement before the use of approved anti-VEGF drugs leaves ophthalmologists in a dilemma.

No large-scale prospective randomized clinical trial has been conducted showing that bevacizumab is superior to the approved anti-VEGF drugs (aflibercept and ranibizumab). The Protocol T study was the only randomized controlled clinical trial that compared bevacizumab with other approved anti-VEGFs for the treatment of DME. In the Protocol T study, aflibercept had superior 2-year visual acuity outcomes compared with bevacizumab among eyes with baseline visual acuity of 20/50 to 20/320, and bevacizumab was not superior to aflibercept and ranibizumab under any circumstances.[17] The superiority of aflibercept over ranibizumab has also not been verified.

Moreover, 75.8% of participants believed that dispensing multiple syringes from a single bevacizumab vial could increase the risk of endophthalmitis and 35.6% felt pressured to use a single bevacizumab bottle for more than one patient, although the reimbursement restrictions are not clear regarding dispensing multiple syringes from a single bevacizumab bottle. The multiple use of bevacizumab from a single bottle remains

a matter of debate. Ng et al.[18] reused vials for a maximum of 10 consecutive injections in their trial and concluded that as long as proper sterile techniques are implemented, using the same vial does not increase the risk of endophthalmitis from intravitreal injections. Das et al.[19] stated that bevacizumab does not lose stability when stored at 4°C and may be used for a week by direct withdrawal from the vial without fear of infection or inflammation if all standard precautions related to intravitreal injection are adhered to. Ornek et al.[20] stated that the storage and reuse of bevacizumab do not seem to result in microbial contamination, and multiple doses of bevacizumab from a single-use vial could be used within 2 weeks. However, an endophthalmitis outbreak in a university hospital was caused by dividing the same single-use bevacizumab into multiple doses. In fact, several endophthalmitis cases have been reported in association with splitting bevacizumab from a single bottle.[21]

Conclusion

Bevacizumab is widely used as a first-line treatment for all indications of anti-VEGF, and reimbursement conditions preclude ophthalmologists' right to treat patients according to their own preferences. Given the current reimbursement situation, it is not possible for doctors to freely choose a patient-specific treatment.

Acknowledgements: The authors express their appreciation to the Turkish Ophthalmological Association for their support. The authors would like to thank Dr. İzzet Can for his support.

Ethics

Ethics Committee Approval: The research protocol was approved by the Institutional Ethics Committee and Review Board of Kocaeli University (number: KAEK 2020/219).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: V.L.K., E.Ö.T., Concept: V.L.K., E.Ö.T., Design: V.L.K., E.Ö.T., Data Collection or Processing: V.L.K., E.Ö.T., Analysis or Interpretation: V.L.K., E.Ö.T., F.Ş., Literature Search: V.L.K., E.Ö.T., Writing: V.L.K., E.Ö.T., F.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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