



DOI: 10.14744/eur.2023.55265
Eur Eye Res 2024;4(1):85–89

EUROPEAN
EYE
RESEARCH

ORIGINAL ARTICLE

Comparison of costs of bevacizumab, ranibizumab, and aflibercept in loading dose administration for diabetic macular edema treatment: Observational cost analysis

 Ali Altan Ertan Boz,  Erkan Celik

Department of Ophthalmology, Sakarya University Training and Research Hospital, Sakarya, Türkiye

Abstract

Purpose: Antivascular endothelial growth factor (anti-VEGF) medications find extensive utilization in addressing diabetic macular edema (DME). In December 2018, the Social Security Institution of Türkiye introduced the requirement of a loading dose of bevacizumab and subsequent unresponsiveness criteria for the application of other intravitreal drugs in retinal diseases. The aim of this study is to perform a cost analysis of bevacizumab use in the loading dose for DME treatment compared to the use of aflibercept and ranibizumab.

Methods: Patients diagnosed with DME between 2019 and 2022, who received three consecutive doses of bevacizumab at 4–6 week intervals, were included in the study. The prices of anti-VEGF drugs were calculated in US dollars (USD) by taking the average of prices for the respective years. The average prices for the bevacizumab vials were 178.28 USD, 153.12 USD, 149.08 USD, and 138.83 USD for the years 2019, 2020, 2021, and 2022, respectively.

Results: A total of 671 eyes were included in the study. The mean age of the patients was 67.8 ± 10.2 (range 42–86) years. The mean best-corrected visual acuity improved from 0.21 ± 0.13 (range 0.05–0.4) before injections to 0.45 ± 0.11 (range 0.2–0.7) after three doses. No cases of retinal tear/detachment or endophthalmitis were observed. The total cost of 2013 doses of bevacizumab administered intravitreally to 671 eyes was 322,894,50 USD. The cost would be 791,640.96 USD if ranibizumab was used and 800,491.53 USD if aflibercept was used.

Conclusion: In the study, it was determined that bevacizumab is more affordable than other anti-VEGF drugs in the treatment of DME. Health-care systems may prefer less costly drugs to use their resources more effectively. However, the final decision in drug selection should always be made by doctors based on effectiveness for the benefit of the patient.

Keywords: Aflibercept; Anti-VEGF; bevacizumab; cost analysis; diabetic macular edema; ranibizumab.

Diabetic retinopathy (DR) stands as a microvascular complication arising from diabetes mellitus (DM). Within DR, the primary contributor to enduring visual impairment is diabetic macular edema (DME).^[1,2] In the pathogenesis of DME, elevated releases of interleukin (IL)-6, IL-8, and vascular

endothelial growth factor (VEGF) contribute significantly, fueling inflammation, angiogenesis, and oxidative stress.^[3] Anti-VEGF drugs are frequently employed as the primary treatment option in patients with DME to improve visual acuity (VA) and reduce central macular thickness (CMT).^[4–6]



Cite this article as: Boz AAE, Celik E. Comparison of costs of bevacizumab, ranibizumab, and aflibercept in loading dose administration for diabetic macular edema treatment: Observational cost analysis. *Eur Eye Res* 2024;1:85–89.

Correspondence: Ali Altan Ertan Boz, M.D. Department of Ophthalmology, Sakarya University Training and Research Hospital, Sakarya, Türkiye
E-mail: alialtanertan@hotmail.com

Submitted Date: 26.08.2023 **Revised Date:** 26.10.2023 **Accepted Date:** 16.11.2023 **Available Online Date:** 20.03.2024

OPEN ACCESS This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).



Bevacizumab, ranibizumab, and aflibercept stand out as the prevailing anti-VEGF agents utilized in the treatment of DME. Bevacizumab (Altuzan 100 mg/4mL[®], Genentech-Roche, South San Francisco, CA, USA) is a monoclonal antibody that blocks all isoforms of VEGF-A.^[7] Ranibizumab (Lucentis 10 mg/mL[®], Genentech-Roche, South San Francisco, CA, USA) is a humanized monoclonal antibody fragment that targets the VEGF-A Fab fragment.^[8] Aflibercept (Eylea 40 mg/mL[®], Regeneron, Eastview, NY, USA) is a human fusion protein that combines elements from the IgG Fc region with VEGF receptor ligand-binding components. This fusion enables it to interact not only with VEGF-A but also with VEGF-B, placental growth factor-1, and -2.^[9]

Studies have shown that the efficacy of anti-VEGF drugs in DME treatment is approximately comparable to each other.^[9-12] Bevacizumab, which is 20–40 times cheaper per injection compared to ranibizumab and aflibercept, is commonly used off-label for DME treatment in the US and Europe.^[13] Anti-VEGF therapy constitutes a significant portion of total health-care expenditures in Europe, leading to a considerable burden on health-care systems due to inadequate cost management.^[13] In December 2018, the Social Security Institution (SSI) of Türkiye introduced the requirement of bevacizumab loading dose and subsequent unresponsiveness criteria for the reimbursement of other intravitreal drugs (aflibercept, ranibizumab, or dexamethasone implant) in retinal diseases.^[14]

The aim of this study is to compare the cost analysis of bevacizumab usage in the treatment of DME with the usage of aflibercept and ranibizumab.

Materials and Methods

This retrospective study was conducted at Sakarya University Training and Research Hospital between February 2019 and December 2022. Ethical approval was obtained from the Sakarya University Faculty of Medicine Ethics Committee (May 02, 2023/161). Each patient provided written informed consent, and the study was carried out in compliance with the principles outlined in the Helsinki Declaration. Bevacizumab loading was administered at a dose of 1.25 mg/0.1 mL in three consecutive doses at 4–6-week intervals. Each patient was administered a vial of bevacizumab to prevent the development of endophthalmitis. After three doses, the criteria for inadequate response were defined as a decrease in visual acuity (VA) or at least one line (5 l) loss compared to baseline and/or CMT not decreasing by 50 microns on optical coherence tomography (OCT).^[14] In case of an

inadequate response, treatment could be continued with other intravitreal drugs. The choice between aflibercept and ranibizumab was made based on the decision of the following doctor during the course of treatment.

Patients newly diagnosed with DME who received three consecutive doses of bevacizumab at 4–6-week intervals were included in the study. All patients diagnosed with DR in our retina unit underwent best-corrected visual acuity (BCVA) measurement using Snellen chart, intraocular pressure measurement with applanation tonometry, anterior and posterior segment examination, CMT measurement using OCT (Cirrus HD, Carl Zeiss Meditec, Dublin, CA, USA), and fundus photography and angiography using a fundus fluorescein angiography device (Canon Sales Co., Inc., Chiba, Japan). Based on these assessments, patients requiring anti-VEGF treatment received intravitreal bevacizumab in three doses at 4–6-week intervals under surgical conditions. In case of an inadequate response, a switch to aflibercept or ranibizumab drugs was made. The pro re nata protocol adopted in EURETINA guidelines was followed.^[15] This protocol involves administering anti-VEGF when intraretinal/subretinal fluid is seen in OCT at monthly follow-ups after the 3-month loading dose.

The prices of anti-VEGF drugs were calculated by taking the average prices for the respective years and converting Turkish Lira (TL) calculations to US Dollars (USD) using the average exchange rate of the Turkish Central Bank for the relevant year. The average prices for bevacizumab 100 mg/4 mL (Altuzan, Genentech, South San Francisco, CA, USA) and vials were 178.28 USD (1012.68 TL), 153.12 USD (1131.71 TL), 149.08 USD (1325.40 TL), and 138.83 USD (2301.89 TL) for the years 2019, 2020, 2021, and 2022, respectively. The average price of ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA) was 458.13 USD (2602.21 TL), 373.51 USD (2618.34 TL), 342.30 USD (3043.05 TL), and 318.39 USD (5279.00 TL) for the years 2019, 2020, 2021, and 2022, respectively. The average price of aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, New York, USA and Bayer Healthcare Pharmaceuticals, Berlin, Germany) was 444.76 USD (2526.28 TL), 403.48 USD (2828.43 TL), 362.25 USD (3220.48 TL), and 336.94 USD (5586.54 TL) for the years 2019, 2020, 2021, and 2022, respectively. The decrease in dollar-based drug prices from 2019 to 2022 is due to the depreciation of the TL against the USD (average USD/TL rates for 2019, 2020, 2021, and 2022 were 5.68, 7.01, 8.89, and 16.58, respectively). The price comparison for dexamethasone implant (Ozurdex; Allergan Inc., Irvine, CA, USA) was not provided in our study because dexamethasone implant was not included in the study.

Statistical Analysis

The data underwent analysis using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and numerical values were presented in the form of mean±standard deviation.

Results

A total of 398 patients with 671 eyes were included in the study, with 321 eyes diagnosed in 2019, 53 eyes in 2020, 103 eyes in 2021, and 194 eyes in 2022. The average age of the patients was 67.8±10.2 (range: 42–86) years. The mean BCVA improved from 0.21±0.13 (range: 0.05–0.4) decimal before injections to 0.45±0.11 (range 0.2–0.7) decimal after three doses. Elevated intraocular pressure controlled with medical treatment was observed in 23 eyes (3.4%). No cases of retinal tear/detachment or endophthalmitis were recorded.

Over 4 years, a total of 2013 doses of bevacizumab were intravitreally administered to 671 eyes, resulting in a cost of 322,894,5 USD. The cost would be 791,640.96 USD if ranibizumab was used and 800,491.53 USD if aflibercept was used. The total number of intravitreal bevacizumab administrations and the total costs of anti-VEGF agents according to the years are presented in Table 1.

Discussion

The increasing elderly population with evolving health-care systems has led to rising costs of SSIs. Therefore, SSIs must ensure more effective utilization of resources to accommodate escalating expenses. The prevalence of DM is on the rise, and by 2045, an estimated 783 million people are projected to be affected by this disease,^[16] resulting in an approximate health-care expenditure of 845 billion USD.^[17] Drug expenditures constitute a significant portion of these costs. The use of anti-VEGF drugs in chronic DM, coupled with a longer life expectancy, has introduced substantial economic burdens. Reports suggest that the intravitreal use of anti-VEGF drugs resulted in a drug expenditure of 447 million pounds in 2015/2016.^[18] Bevacizumab's cost is 20–40 times lower than that of ranibizumab, and it is estimated that in the Netherlands

alone, ranibizumab use for DME treatment would lead to approximately 10–15 million Euros higher costs compared to bevacizumab.^[19] Researchers have suggested that switching to bevacizumab for all anti-VEGF agents could result in savings of around 18 billion USD over a 10-year period.^[20] Another study indicated that the number of patients requiring anti-VEGF treatment and the economic burden associated with it has increased over the years, with bevacizumab use expected to alleviate this burden.^[21]

Bevacizumab is widely used off-label intravitreally in the United States and Europe, and it has become a standard treatment for DME in the Netherlands since 2009.^[19] Studies have shown the efficacy and reliability of bevacizumab in DME treatment.^[11,12,22] Bevacizumab has been reported to provide similar improvements in visual acuity and significant reductions in CMT as reported for ranibizumab. In the protocol T study, after 2 years, bevacizumab, aflibercept, and ranibizumab demonstrated similar efficacy and number of injections in eyes with visual acuity between 20/32 and 20/40.^[9] However, the cost-effectiveness analysis of the protocol T study found that even considering different cost-effectiveness models such as longer duration of effect, lower adverse event rates, or quality-adjusted gain in visual acuity over the years, aflibercept or ranibizumab were not cost-effective compared to bevacizumab.^[20] Administering bevacizumab as a primary treatment for DME could significantly reduce costs. In our study, the 4-year cost of bevacizumab administered in the loading dose was found to be approximately 2,5 times cheaper in USD compared to ranibizumab and aflibercept.

Ophthalmologists have reported that they pay careful attention to legal and ethical considerations when choosing anti-VEGF treatments and that they are sometimes forced to choose expensive agents due to the lack of legal basis.^[18] The decision of the Turkish SSI and the subsequent approval of bevacizumab's intravitreal use by the Turkish Medicines and Medical Devices Agency in 2019 suggest that ophthalmologists in Türkiye will have more legal leeway. Following these decisions, we anticipate a decrease in the cost burden of anti-VEGF treatments on the SSI in Türkiye.

Table 1. Total intravitreal bevacizumab administrations and costs of anti-VEGF drugs according to the years

Year/anti-VEGF drugs	2019 (N/n) 321/963	2020 (N/n) 53/159	2021 (N/n) 103/309	2022 (N/n) 194/582	Total (N/n) 671/2013
Bevacizumab (USD)	171.683,64	24.346,08	46.065,72	80.799,06	322.894,50
Ranibizumab (USD)	441.179,19	59.388,09	105.770,7	185.302,98	791.640,96
Aflibercept (USD)	428.303,88	64.153,32	111.935,3	196.099,08	800.491,53

USD: United States Dollar; N: Number of eyes; n: Number of intravitreal injections administered.

The limitations of our study include considering only the costs of drug treatment, without accounting for other expenses such as direct medical costs and application costs. Additionally, a comparison was made solely based on the prices of anti-VEGF agents; a cost-effectiveness evaluation that takes into account not only the drug prices but also their effectiveness was not conducted. Another limitation is the exclusion of post-loading dose anti-VEGF administrations. Conducting further studies with a larger number of patients over longer periods, including post-loading dose anti-VEGF administrations, and conducting a cost-effectiveness evaluation would be beneficial in calculating the cost-effectiveness of bevacizumab.

Conclusion

Following the decisions of the SSI and the Turkish Medicines and Medical Devices Agency, the legal basis for bevacizumab's intravitreal use in Türkiye is established. Our study demonstrated that bevacizumab is affordable compared to other anti-VEGF agents. Therefore, the intravitreal use of bevacizumab in Türkiye is expected to reduce the cost burden of anti-VEGF treatments on the SSI. However, the final decision in drug selection should always be made by doctors based on effectiveness for the benefit of the patient.

Ethics Committee Approval: This study was approved by Sakarya University Faculty of Medicine Ethics Committee (Date: April 10, 2023; Number: 161).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: A.A.E.B.; Design: A.A.E.B.; Supervision: A.A.E.B.; Resource: A.A.E.B.; Materials: A.A.E.B.; Data collection and/or processing: A.A.E.B.; Analysis and/or interpretation: A.A.E.B., E.Ç.; Literature search: A.A.E.B., E.Ç.; Writing: A.A.E.B.; Critical review: A.A.E.B., E.Ç.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

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

References

1. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: Global prevalence, major risk factors, screening practices and public health challenges: A review. *Clin Exp Ophthalmol* 2016;44:260–77. [CrossRef]
2. Miller K, Fortun JA. Diabetic macular edema: Current understanding, pharmacologic treatment options, and developing therapies. *Asia Pac J Ophthalmol (Phila)* 2018;7:28–35.
3. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology* 2009;116:73–9. [CrossRef]
4. Sun JK, Jampol LM. The diabetic retinopathy clinical research network (DRCR.net) and its contributions to the treatment of diabetic retinopathy. *Ophthalmic Res* 2019;62:225–30. [CrossRef]
5. Naujokaitis T, Balciuniene VJ. Real-world treatment patterns and vision outcomes with ranibizumab for diabetic macular edema. *J Ophthalmol* 2021;2021:8825082. [CrossRef]
6. Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: A network meta-analysis. *Cochrane Database Syst Rev* 2018;10:CD007419. [CrossRef]
7. Bevacizumab. Anti-VEGF monoclonal antibody, avastin, rhumab-VEGF. *Drugs R D* 2002;3:28–30. [CrossRef]
8. Witmer AN, Vrensen GF, Van Noorden CJ, Schlingemann RO. Vascular endothelial growth factors and angiogenesis in eye disease. *Prog Retin Eye Res* 2003;22:1–29. [CrossRef]
9. Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: Recent clinically relevant findings from DRCR.net Protocol T. *Curr Opin Ophthalmol* 2017;28:636–43. [CrossRef]
10. Wells JA, Glassman AR, Jampol LM, Aiello LP, Antoszyk AN, Baker CW, et al. Association of baseline visual acuity and retinal thickness with 1-year efficacy of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema. *JAMA Ophthalmol* 2016;134:127–34. [CrossRef]
11. Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, Yaseri M, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;116:1142–50. [CrossRef]
12. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: Report 2. *Ophthalmology* 2010;117:1078–86.e2. [CrossRef]
13. Levinson DR. Medicare Payments for Drugs Used to Treat Wet Age-Related Macular Degeneration. Washington, DC: Office of the Inspector General; 2012.
14. Sosyal Güvenlik Kurumu Sağlık Uygulama Tebliği. Available from: https://www.sgk.gov.tr/wps/portal/sgk/tr/kurumsal/merkez-teskilati/ana_hizmet_birimleri/gss_genel_mudurlugu/anasayfa_duyurular/guncel_sut_28122018. Sep 15, 2023.
15. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the management of diabetic macular edema by the European society of retina specialists (EURETINA). *Ophthalmologica* 2017;237:185–222. [CrossRef]
16. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022;183:109119.

17. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2020;162:108072. [\[CrossRef\]](#)
18. Hollingworth W, Jones T, Reeves BC, Peto T. A longitudinal study to assess the frequency and cost of antivasular endothelial therapy, and inequalities in access, in England between 2005 and 2015. *BMJ Open* 2017;7:e018289. [\[CrossRef\]](#)
19. Schauwvlieghe AM, Dijkman G, Hooymans JM, Verbraak FD, Hoyng CB, Dijkgraaf MG, et al. Comparing the effectiveness and costs of bevacizumab to ranibizumab in patients with diabetic macular edema: A randomized clinical trial (the BRDME study). *BMC Ophthalmol* 2015;15:71. [\[CrossRef\]](#)
20. Ross EL, Hutton DW, Stein JD, Bressler NM, Jampol LM, Glassman AR. Cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema treatment analysis from the diabetic retinopathy clinical research network comparative effectiveness trial. *JAMA Ophthalmol* 2016;134:888–96. [\[CrossRef\]](#)
21. Atum M, Çakır B, Yuvacı İ, Çelik E, Alagöz G. The frequency and costs of intravitreal therapy agents in retinal diseases. *Ophthalmol J* 2020;5:55–9. [\[CrossRef\]](#)
22. Nicholson BP, Schachat AP. A review of clinical trials of anti-VEGF agents for diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2010;248:915–30. [\[CrossRef\]](#)