Outcomes of three intravitreal injections of bevacizumab given monthly for diabetic macular oedema is a viable treatment for an economically disadvantaged population

**Introduction**

Diabetic macular oedema (DMO) is the most common cause of visual impairment amongst diabetic patients.\(^1\)\(^2\) The treatment of DMO has evolved over time as our understanding of the pathogenesis of DMO has increased. The demonstration of higher levels of vascular endothelial growth factor (VEGF) in the vitreous samples of eyes with DMO prompted the use of intravitreal injection (IVI) of approved anti-vascular endothelial growth factor (VEGF) is costly and hence off label use of bevacizumab is practiced in spite of concerns about its safety.

**Background:** The treatment of diabetic macular oedema (DMO) by intravitreal injection (IVI) of approved anti-vascular endothelial growth factor (VEGF) is costly and hence off label use of bevacizumab is practiced in spite of concerns about its safety.

**Aim:** To examine the effect of three IVI of bevacizumab given monthly, on best corrected visual acuity (BCVA) and central foveal thickness (CFT) of eyes with DMO.

**Setting:** Charity hospital attached to a medical college in India.

**Methods:** Patients with centre involving DMO with BCVA ≤ 6/9 and CFT ≥ 260 microns were recruited prospectively, and three IVI bevacizumab given monthly (from a common vial). At four months BCVA and CFT were assessed and compared with baseline data. Side effects, if any, were recorded. Best corrected visual acuity was converted to logMAR units for statistical analysis. Student’s \(t\)-test were conducted to see statistically significant changes in BCVA and CFT.

**Results:** A total of 50 eyes of 38 patients received three monthly IVI bevacizumab. Best corrected visual acuity (logMAR) improved from baseline mean of 0.80 ± 0.49 to final mean of 0.51 ± 0.36, which was significant (\(p = 0.0001\)). The mean baseline CFT (\(\mu m\)) improved from 448.40 ± 149.47 to 368.76 ± 131.49, which was significant (\(p = 0.0001\)). No cases of endophthalmitis were reported. Various factors such as diabetes duration and HbA1c (hemoglobinA1c) value were not found to be significant for the improvement in BCVA and CFT.

**Conclusion:** Intravitreal injection bevacizumab given as three monthly injections was safe, economical and effective in the management of DMO.

**Keywords:** diabetic macular oedema; anti vascular endothelial growth factor; bevacizumab; intravitreal; off label use.

---

**Outcomes of three intravitreal injections of bevacizumab given monthly for diabetic macular oedema is a viable treatment for an economically disadvantaged population**

**Authors:**
Aazambir S. Brar\(^1\)
Vivek B. Wani\(^1\)
Arvind L. Tenagi\(^1\)

**Affiliations:**
\(^1\)Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital & MRC, Belagavi, India

**Corresponding author:**
Vivek Wani, vbwani@yahoo.com

**Dates:**
Received: 25 Sept. 2020
Accepted: 01 Feb. 2021
Published: 28 Apr. 2021

**How to cite this article:**
Brar A.S, Wani V.B, Tenagi A.L. Outcomes of three intravitreal injections of bevacizumab given monthly for diabetic macular oedema is a viable treatment for an economically disadvantaged population. Afr Vision Eye Health. 2021;80(1), a618. https://doi.org/10.4102/aveh.v80i1.618

**Copyright:**
© 2021. The Author(s). Licensee: AOSIS. This work is licensed under the Creative Commons Attribution License.

---

**Read online:**
Scan this QR code with your smart phone or mobile device to read online.
However, preparation of multiple aliquots or repeated withdrawal of bevacizumab from a 4 mL vial is subjected to risk of contamination and clusters of endophthalmitis because of IVI bevacizumab have been reported.\(^6\,\,^9\)

However, as one vial of ranibizumab costs nearly INR22,000.00 (Indian rupee) (equivalent to $297.00) in India compared with INR1500.00 (equivalent to $19.00) for one dose of bevacizumab drawn from a multi-dose vial, it has economical advantage in countries such as India where most patients are not able to afford ranibizumab. In the United States, it is reported that one dose of ranibizumab costs $1543.00 compared with $43.00 for one dose of bevacizumab.\(^9\)

Bevacizumab is the most commonly used anti VEGF for the treatment of DMO and other retinal vascular disorders such as neovascular age related macular degeneration (NAMD), macular oedema because of retinal vein occlusions and myopic choroidal neovascular membranes in our institute because of economic reasons. In this study, we report the efficacy and safety of three IVI of bevacizumab given monthly for the treatment of DMO and its effect on central foveal thickness (CFT) as measured by optical coherence tomography (OCT).

**Methods**

This was a single centre, prospective, non-comparative and interventional study conducted in the Department of Ophthalmology of Karnataka Lingayat Education Society (KLES) Dr. Prabhakar Kore Hospital and Medical Research Centre, a multi-speciality hospital based in a rural area of southern India. This is a teaching hospital attached to Jawaharlal Nehru Medical College, KLE (Karnataka Lingayat Education Society) Academy of Higher Education and Research, Belagavi, Karnataka, India.

Patients for the study were prospectively recruited from those diabetic patients attending the out-patient eye clinic of our hospital. The criteria for inclusion were patients with type II diabetes mellitus (DM) aged between 25 years and 75 years who were able to give informed consent for the study and were having centre involving DMO with particular reference to the type of diabetes mellitus (DM) and its duration, treatment for DM, history of hypertension, ischemic heart disease, stroke, renal involvement and other morbidities were noted. A detailed ocular history was taken to note duration of visual deterioration, affected eye and history of treatment including any ocular surgery.

All the recruited patients underwent detailed ocular examination that included assessment of BCVA on the Snellen chart, slit lamp biomicroscopic examination with particular attention to detect neovascularisation of the iris and observing the status of the lens, measurement of intraocular pressure by Goldmann applanation tonometry and detailed fundus examination. Diabetic retinopathy (DR) was classified on the basis of fundus examination and according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) guidelines.\(^1\)

The presence of DMO and if it involved the macular centre were assessed. All the recruited patients underwent OCT examination with spectral domain OCT using macular scan and line scan programmes after pupilary dilatation. The CFT was the mean thickness of the innermost circle of 1 mm diameter in the macular scan, which was recorded.

The patients who were eligible for the study received the IVI of bevacizumab within 10 days of recruitment. All IVI procedures were carried out in the operating theatre. The eye to be injected was dilated with commercially available preparation of tropicamide 0.8% with phenylephrine 5% instilled twice at 15 min interval. The surgeon always scrubbed and wore sterile gloves for the procedure. In the operation theatre, topical proparacaine hydrochloride 0.5% and povidone iodine 5% were instilled in the eye alternately for three times at 2 min interval. The circulating nurse brought the bevacizumab vial stored in the refrigerator and cleaned the rubber cap with povidone iodine 10% and alcohol swab 70% and it for withdrawal. The surgeon withdrew 0.1 mL of the drug in a single use sterile 31 g BD (bis in die [twice daily]) U-100 insulin syringes (BD Medical-Diabetes care, United States of America) and adjusted the dose to 0.05 mL.

If there were more than one patient, then that many numbers of syringes were loaded taking care to clean the rubber cap of the vial each time with povidone iodine 10% and alcohol swab 70%. The loaded syringes were kept on a sterile tray. After withdrawal of the drug in required number of syringes, the rubber cap of the bevacizumab vial was again cleaned with povidone iodine 10% and alcohol swab 70% and kept in the refrigerator. In this way, the vial was used for up to a total of 20 withdrawals and then discarded. Usually this happened within 30 days.

---

**Reference**

1. The name, age, sex, addresses and contact details of the recruited patients were recorded. A detailed medical history with particular reference to the type of diabetes mellitus (DM) and its duration, treatment for DM, history of hypertension, ischemic heart disease, stroke, renal involvement and other morbidities were noticed. A detailed ocular history was taken to note duration of visual deterioration, affected eye and history of treatment including any ocular surgery.

2. All the recruited patients underwent detailed ocular examination that included assessment of BCVA on the Snellen chart, slit lamp biomicroscopic examination with particular attention to detect neovascularisation of the iris and observing the status of the lens, measurement of intraocular pressure by Goldmann applanation tonometry and detailed fundus examination. Diabetic retinopathy (DR) was classified on the basis of fundus examination and according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) guidelines.\(^1\)

3. The presence of DMO and if it involved the macular centre were assessed. All the recruited patients underwent OCT examination with spectral domain OCT using macular scan and line scan programmes after pupilary dilatation. The CFT was the mean thickness of the innermost circle of 1 mm diameter in the macular scan, which was recorded.

4. The patients who were eligible for the study received the IVI of bevacizumab within 10 days of recruitment. All IVI procedures were carried out in the operating theatre. The eye to be injected was dilated with commercially available preparation of tropicamide 0.8% with phenylephrine 5% instilled twice at 15 min interval. The surgeon always scrubbed and wore sterile gloves for the procedure. In the operation theatre, topical proparacaine hydrochloride 0.5% and povidone iodine 5% were instilled in the eye alternately for three times at 2 min interval. The circulating nurse brought the bevacizumab vial stored in the refrigerator and cleaned the rubber cap with povidone iodine 10% and alcohol swab 70% and it for withdrawal. The surgeon withdrew 0.1 mL of the drug in a single use sterile 31 g BD (bis in die [twice daily]) U-100 insulin syringes (BD Medical-Diabetes care, United States of America) and adjusted the dose to 0.05 mL.

5. If there were more than one patient, then that many numbers of syringes were loaded taking care to clean the rubber cap of the vial each time with povidone iodine 10% and alcohol swab 70%. The loaded syringes were kept on a sterile tray. After withdrawal of the drug in required number of syringes, the rubber cap of the bevacizumab vial was again cleaned with povidone iodine 10% and alcohol swab 70% and kept in the refrigerator. In this way, the vial was used for up to a total of 20 withdrawals and then discarded. Usually this happened within 30 days.

---

**Conclusion**

This study has shown that multiple IVI of bevacizumab is safe and effective for the treatment of DMO. It is a good alternative to ranibizumab due to its lower cost and ease of use in a resource-poor setting.
The procedure of injection was as follows. The eye was painted with povidone iodine 10% and draped. A sterile speculum was inserted, and a sterile cotton bud soaked in proparacaine hydrochloride 0.5% was held at injection site for 30 s followed by cotton bud soaked in povidone iodine 5% was applied at the injection site. Then, the 0.05 mL bevacizumab containing 1.25 mg of the drug injected through the pars plana at a distance of 3.5 mm in pseudophakic or aphakic eyes and 4 mm in phakic eyes, respectively. A sterile caliper was used to mark the distance at which injection was to be made. The injection was given in the supero-temporal quadrant in all the cases.

After the injection, the site of injection was held pressed for 30 s with a cotton bud and the globe was checked for hardness and then a drop of povidone iodine 5% was instilled and the eye was patched for 4 h. No post-operative topical or systemic antibiotics were prescribed, and the patient was reviewed after 1 week and then 4 weeks after the injection. Patients were instructed to report earlier if they experienced any pain or diminished vision. Patient was scheduled for the next injection usually at 28–35 days’ time after the last injection.

Patients underwent a thorough ocular examination at the visit after one month of each injection and ocular examinations were carried out as described here. Special care was taken to detect rise in intraocular pressure (IOP), signs of anterior chamber activity, vitritis, injury to the lens, retinal tears, retinal detachment or vitreous haemorrhage. All patients received three injections at monthly intervals and at the end of one month after the last injection, complete ocular examination with BCVA, IOP and OCT examination was performed. The CFT was recorded from macular scan.

Statistical analysis
The data were entered in an Excel sheet and Snellen visual acuity was converted into logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. The main outcomes studied were the difference between (1) initial and final BCVA (2) initial and final CFT and (3) initial and final IOP. The statistical analysis was carried out with student’s t-tests using the Statistical Package for Social Sciences (SPSS) software version 20.0 (SPSS Inc., United States [US]). We also examined if any variable was significant for improvement of BCVA by two (2) Snellen lines or more and reduction in CFT by 50 μm or more. P-value of less than 0.05 was regarded as significant.

Ethical considerations
Approval to conduct the study was received from Jawaharlal Nehru Medical College Institutional Ethics Committee on Human Subjects Research, Jawaharlal Nehru Medical College, Belagavi (MDC/DOME/66).

Results
A total of 50 eyes of 38 patients were eligible to be included in the study as they had completed three IVI at monthly intervals and follow up of 4 months. There were 31 males (81.6%) and the average age of the patients was 61.1 years (range 38–75 years, standard deviation [SD] 9.0). A total of 12 patients who had bilateral DMO, received IVI in both eyes and 26 patients received IVI in only one eye.

All patients were suffering from type 2 DM and the mean duration of diabetes was 12.35 ± 7.6 years (range: 7 months to 30 years). A total of 23 patients (60.5%) were on oral hypoglycemic agents, 6 (15.8%) on insulin therapy and 9 (23.7%) patients were receiving both insulin and oral hypoglycemic agents for their diabetes. The control of DM in our cohort was unsatisfactory as seen in average HbA1c of 8.81% ± 1.04 (range: 7–11.4). Many patients had systemic comorbidities such as hypertension in 20 (52.6%), hypercholesterolemia in nine (23.7%) and nephropathy in six (15.8%). A total of 11 patients (28.9%) were smokers.

The ocular features in the 50 eyes included pseudophakia in 13, phakic in 37, glaucoma on medication in one eye and history of pan retinal photocoagulation more than 4 months ago in nine (18%) eyes. The diagnosis of DR was mild non-proliferative DR (NPDR) in one eye, moderate NPDR in eight eyes, severe NPDR in 19 eyes and with past pan retinal photocoagulation in nine eyes (bilateral in three patients) and non-high risk characteristic PDR in 13 eyes.

There were various systemic comorbidities observed in 38 patients of the cohort (Table 1).

The average baseline BCVA and final BCVA were 0.80 ± 0.48 logMAR (range: 0.17–1.77) and 0.50 ± 0.36 logMAR (range: 0.17–1.47), respectively, and the difference was statistically significant (p = 0.0001). Similarly, the average baseline CFT and the final CFT were 449.4 ± 148.1 μm (range: 275–925) and 368.8 ± 131.5 μm, respectively, and the difference was statistically significant (p = 0.0001) (Table 2). There was no significant difference between initial and final average IOP of the 50 eyes (Table 2).

A total of 19 (38%) eyes improved vision by two or more lines and one-line improvement was seen in 30 (60%) eyes. One eye did not show any improvement after three injections and none had worsening of the vision.

We wanted to see the role of variables such as age, sex, duration of DM, level of initial HbA1c and the presence of comorbidities in improvement in BCVA by two or more lines

| Comorbidities          | Present n | Present % | Absent n | Absent % |
|------------------------|-----------|-----------|----------|----------|
| Hypertension           | 20        | 52.6      | 18       | 47.4     |
| Anticoagulant therapy  | 4         | 10.5      | 34       | 89.5     |
| Hypercholesterolemia   | 9         | 23.7      | 29       | 76.3     |
| Nephropathy            | 6         | 15.8      | 32       | 84.2     |
| Smoking                | 11        | 28.9      | 27       | 71.1     |

Note: Percentage of comorbidities present (n = 38 patients).
and reduction of CFT by 50 μm or more. However, the univariate analysis did not show any variable to be significant for improvement of BCVA by two or more lines or reduction in CFT of 50 μm or more.

Complications included subconjunctival haemorrhage in seven eyes (14%), corneal epithelial defect in two eyes (4%) and anterior chamber reaction of grade 2 in one eye (2%). All complications were conservatively managed and they did not have any effect on visual acuity. None of the patients had lens injury, retinal detachment, vitreous haemorrhage, endophthalmitis or retinal tears. No systemic adverse effects were reported by the patients.

Discussion

India has a very high rate of DM amongst adults aged 20 years and above with the second highest number of cases of DM in the world and a projected number of 101 million cases of DM by the year 2030.12 With increasing number of diabetic population, the vision threatening complications of DR such as DMO and PDR will cause economic burden on the society. Hence, it is important to explore economical and effective treatment strategies for vision threatening complications of DR. In this context our study shows the safety and efficacy of three IVI of bevacizumab given monthly in cases of DMO with selection criteria of the study.

The treatment of DMO has evolved over time according to evidence-based medicine. Early Treatment of DR Study showed in a randomised clinical trial that, focal or grid laser photocoagulation was superior to observation only, in cases with clinically significant macular oedema.13 In the early 2000s, studies showed that IVI of triamcinolone acetonide was effective in treating DMO and was comparable to laser photocoagulation therapy.14,15 However, soon it was realised that intravitreal triamcinolone acetonide injection was not superior in terms of visual results and also led to complications of increased IOP and development of cataract in significant number of patients needing medical or surgical intervention.16

The interest in anti VEGF agents as modalities of treatment for DMO led to randomised controlled studies that showed an anti VEGF drug ranibizumab was better than sham injections in the treatment of DMO.4 A Diabetic Retinopathy Clinical Research (DRCR) Network study demonstrated that prompt treatment of DMO with IVI of ranibizumab was better than laser photocoagulation (Protocol I study).17

Many investigators reported off label use of IVI of bevacizumab in place of ranibizumab for the treatment of DMO and validated its efficacy with or without comparison to laser treatment.6,18 The off label use of bevacizumab for IVI in cases of DMO is routinely practiced the world over.

A new anti VEGF known as aflibercept (Eylea, Regeneron, United States of America), which acts as VEGF trap was investigated for its efficacy in DMO and was shown to be effective in the treatment of DMO.19

A DRCR network conducted study compared the efficacy of ranibizumab, aflibercept and bevacizumab for the treatment of centre involving DMO and reported that, at the end of two years, the three anti VEGF drugs were similar in terms of visual gains in eyes with good initial visual acuity.7 However, in eyes with poor initial vision (20/50 or worse), only aflibercept and not ranibizumab was better than bevacizumab in terms of visual gains at the end of two years.7 The analysis of costs involved and the visual acuity gains made by the three anti VEGF drugs in the given study showed that both ranibizumab and aflibercept were not cost-effective compared with bevacizumab in the treatment of DMO.20

Our study clearly shows that monthly IVI of bevacizumab for 3 months is a good economic treatment for DMO in our population.

Our cohort had male preponderance (81.6%), which is higher than that observed in studies by Vyas et al.21 Some studies have shown that males are more prone to develop DMO than females.22 In our study it could be because of inaccessibility of diabetic care for women of our rural region because of social, economic or logistic factors.

Many cases of our cohort were having comorbidities such as hypertension, nephropathy and hypercholesterolemia, which have been shown to increase the risk of DMO.23

### Table 2: Comparison of initial and final best corrected visual acuity, central foveal thickness and intraocular pressure by dependent t-tests.

| Parameters | Mean | SD | Mean difference | SD difference | Percentage of change | Paired t | P |
|------------|------|----|----------------|--------------|---------------------|----------|---|
| BCVA       | 0.80 | 0.49 | 0.29 | 0.21 | 36.09 | 9.6104 | 0.0001* |
| Final      | 0.51 | 0.36 | - | - | - | - | - |
| CFT (μm)   | 448.40 | 149.47 | 79.64 | 69.21 | 17.76 | 8.1369 | 0.0001* |
| Initial    | 368.76 | 131.49 | - | - | - | - | - |
| Final      | 15.68 | 2.76 | 0.25 | 2.66 | 1.61 | 0.6701 | 0.5060 |

SD, standard deviation; BCVA, best corrected visual acuity; CFT, central foveal thickness; IOP, intraocular pressure.

* p < 0.05.
The improvement in visual acuity and reduction in CFT were statistically significant at the end of 4 months from recruitment after three IVI of bevacizumab in our study. All the patients except one showed improvement of at least one line of Snellen acuity in our study. Bevacizumab or laser therapy (BOLT) study, which had administered 3–9 IVI of bevacizumab also observed significant improvement of visual acuity and reduction in CFT.23–25 Solaiman et al. who used an average of 3.3 IVI of bevacizumab also reported similar results.24 Our study showed outcomes similar to several studies (Table 3).

Diabetic macular oedema is unfortunately a chronic disease and tends to recur in many patients after stopping treatment with IVI of any anti VEGF. Patients who receive more number of IVI in the first year of treatment improve visual acuity significantly.4

The Protocol-T 5 year follow up study which showed that the initial visual acuity gains are partially lost after the frequency of IVI of anti VEGF was reduced between third and fifth year of the follow up study. It is pertinent to note that patients received more than 10 injections in the first year of clinical trials.4,29

However, it is difficult to emulate the protocols of clinical trials in real life scenario. In India, it is much more difficult with IVI of ranibizumab and aflibercept because of their cost. In a study of patients who did not adhere to regimen of IVI of anti VEGF, it was shown that non-affordability and poor response to treatment were the main reasons.30

So, in such circumstances, treatment of DMO with IVI of bevacizumab is the best option for economically disadvantaged populations.

The safety of multiple withdrawals of bevacizumab from the same vial is a concern as contamination can occur and lead to cases of endophthalmitis. However, many authors have shown that the rate of endophthalmitis is low with this method.31,32 The rate of endophthalmitis after IVI of anti VEGF can vary from 0.01% to 0.41%.31,32,33,34,35,36

Fintak et al. and Shah et al. did not find any difference in rates of endophthalmitis between bevacizumab and ranibizumab.32,36

However, risks of contamination resulting in clusters of endophthalmitis in cases of withdrawal of bevacizumab from the same vial have been reported.9 In the United States, the aliquots of bevacizumab are prepared by pharmacy according to guidelines of US Pharmacopeia.39

But in spite of such strict adherence, clusters of endophthalmitis have occurred in United States because of contamination in the pharmacy. Also, the facilities of compounding bevacizumab in separate syringes in the pharmacy are not available in most areas of India. Hence, it is very important to follow strict aseptic methods, including cleaning of the rubber cap of the vial with povidone iodine 10% and alcohol swab 70% as followed in our study.

Shortcomings of our study are the small number of cases, short period of follow up and no comparative samples. However, most of the studies involving bevacizumab have small number of cases.21,23,24,25,26

### Conclusion

Our study shows that three IVI of bevacizumab given monthly is effective in treatment of DMO. All except one showed improvement in BCVA at the end of 4 months. Most of the patients showed reduction in CFT indicating the effectiveness of IVI of bevacizumab. We did not encounter any serious side effects in our study.

### Acknowledgements

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

### Authors’ contributions

A.S.B., V.B.W. and A.L.T. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

### Funding information

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
Data availability statement
Data sharing is not applicable to this study.

Disclaimer
The views and opinions expressed in this article are those of the authors and do not necessarily reflect official policy or position of any affiliated agency of the authors.

References
1. Moss SE, Klein BEK. The 14-year incidence of visual loss in a diabetic population. Ophthalmology. 1998;105(6):998–1003. https://doi.org/10.1016/1642-4898(98)90265-0
2. You JW, Rogers SL, Kawaski R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(5):566–564. https://doi.org/10.2337/dc11-1909
3. Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of bevacizumab in patients with diabetic macular edema. Ophthalmology. 2003;110(9):1690–1696. https://doi.org/10.1016/S0161-6420(03)00568-2
4. Nguyen GD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: Results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789–801. https://doi.org/10.1016/j.ophtha.2011.12.039
5. Asten F van, Michels CTJ, Hoyng CB, et al. The cost-effectiveness of bevacizumab, ranibizumab and aflibercept for the treatment of age-related macular degeneration – A cost-effectiveness analysis from a societal perspective. PloS One. 2018;13(5):e0197670. https://doi.org/10.1371/journal.pone.0197670
6. Rajendram R, Fraser-Bell S, Kaines, A. et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: Report 3. Arch Ophthalmol. 2012;130(8):972–979. https://doi.org/10.1001/archophthalmol.2012.393
7. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. Ophthalmology. 2016;123(6):1351–1359. https://doi.org/10.1016/j.ophtha.2016.02.022
8. Goldberg RA, Flynn HW, Miller D, Gonzalez S, Isom RF. Streptococcus pneumoniae endophthalmitis outbreak after intravitreal injection of bevacizumab: One-year outcomes and investigative results. Ophthalmology. 2013;120(7):1448–1453. https://doi.org/10.1016/j.ophtha.2012.12.006
9. Khan, P, Khan, L, Mondal P. Cluster endophthalmitis following multiple intravitreal bevacizumab injections from a single use vial. Indian J Ophthalmol. 2016;64(9):694. https://doi.org/10.1016/j.ijyo.2016.03.014
10. Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: An analysis of the 100% 2008 Medicare fee-for-service part b claims file. Am J Ophthalmol. 2011;151(5):887–895.e1. https://doi.org/10.1016/j.ajodo.2011.11.017
11. Diabetic retinopathy study. Report number 6. Design, methods, and baseline results. Report number 7. A modification of the Airlie House classification of diabetic retinopathy. Prepared by the diabetic retinopathy. Invest Ophthalmol Vis Sci. 1981;21(1 Pt 1):21–226.
12. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011;94(3):311–321. https://doi.org/10.1016/j.diabres.2011.10.029
13. Photoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796–1806. https://doi.org/10.1001/archophthalmol.1985.01001200101S
14. Norlali M, Bakiah S, Zainana E. Intravitreal triamcinolone versus laser photoagulation as a primary treatment for diabetic macular oedema – A comparative pilot study. BMC Ophthalmol. 2011;11(1):36. https://doi.org/10.1186/1471-2415-11-36
15. Massin P, Audren F, Haouchine B, et al. Intravitreal triamcinolone acetoneid for diabetic diffuse macular edema: Preliminary results of a prospective controlled trial. Ophthalmology. 2004;111(2):218–224. https://doi.org/10.1016/j.ophtha.2003.05.037
16. Grover D, Li TJ, Chong CCW. Intravitreal steroids for macular edema in diabetes. Cochrane Database Syst Rev. 2008;(1):CD005656. https://doi.org/10.1002/14651858.CD005656.pub2
17. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117(6):1064–1077.e35. https://doi.org/10.1016/j.ophtha.2010.02.031