Efficacy and Safety of Intravitreal Injection Ranibizumab versus Triamcinolone Acetonide in Diabetic Macular Oedema - A Prospective Randomized Study, Gorakhpur, Uttar Pradesh

Ramyash Singh Yadav[1], Ram Kumar Jaiswal[2], Punita Tripathi[3], Mridula Ranjan[4], Chiranji Rai[5]

[1, 2, 3, 4, 5] Department of Ophthalmology, B.R.D. Medical College, Gorakhpur, Uttar Pradesh, India.

ABSTRACT

BACKGROUND

Diabetic macular oedema is a sight threatening complication of diabetic retinopathy. Vascular endothelial growth factor (VEGF) plays an important role in developing diabetic macular oedema. There are many treatment options available for diabetic macular oedema such as laser therapy, intravitreal injectable medications like anti-VEGF and steroids. This study intends to compare the efficacy and safety of intravitreal injection Ranibizumab (anti-VEGF) and Triamcinolone acetonide (steroid) in diabetic macular oedema.

METHODS

This is a prospective randomized study conducted among 42 patients ≥ 18 years of age with diabetic macular oedema presenting to outpatient department in a tertiary care centre in Gorakhpur, UP, conducted from November 2019 – December 2020. 42 participating patients were divided into 2 groups, A and B with 21 patients in each group. Group A treated with intravitreal injection Ranibizumab (0.05 ml ; 0.50 mg) and group B treated with intravitreal injection Triamcinolone acetonide (4 mg in 0.1 ml). All patients were followed-up at 2 week and 4 week after injection for best corrected visual acuity, intraocular pressure, foveal and para-foveal thickness. Optical coherence tomography was performed for measuring foveal and para-foveal thickness.

RESULTS

The mean age group being 56.48 years in group A and 58.63 years in group B with 12 male and 9 female patients in group A and 10 male and 11 female patients in group B with no dropout during study period. Both injections were equally effective in reducing foveal and para-foveal thickness and improving best corrected visual acuity. Intraocular pressure (IOP) was stable in Ranibizumab treated group but Triamcinolone treated group showed raised IOP in few patients, required anti-glaucoma medications.

CONCLUSIONS

Both treatment types had good efficacy in reducing foveal and para-foveal thickness and thus improving best corrected visual acuity, but intravitreal Ranibizumab is safer and well tolerated along with good efficacy in patients with diabetic macular oedema.

KEYWORDS

Best Corrected Visual Acuity, Diabetic Macular Oedema, Foveal and Para-Foveal Thickness, Intravitreal Ranibizumab, Intravitreal Triamcinolone Acetonide

Corresponding Author:
Dr. Mridula Ranjan,
Department of Ophthalmology,
B.R.D. Medical College,
Gorakhpur, Uttar Pradesh, India.
E-mail: mridularanjan8@gmail.com

DOI: 10.18410/jebmh/2021/453

How to Cite This Article:
Yadav RS, Jaiswal RK, Tripathi P, et al. Efficacy and safety of intravitreal injection ranibizumab versus triamcinolone acetonide in diabetic macular oedema- a prospective randomized study, Gorakhpur, Uttar Pradesh. J Evid Based Med Healthc 2021;8(27):2444-2450. DOI: 10.18410/jebmh/2021/453

Submission 28-04-2021,
Peer Review 05-05-2021,
Acceptance 24-05-2021,
Published 05-07-2021.

Copyright © 2021 Ramyash Singh Yadav et al. This is an open access article distributed under Creative Commons Attribution License [Attribution 4.0 International (CC BY 4.0)]

BACKGROUND

Diabetic macular edema (DME) is an important cause of vision loss in diabetic patients present in 20 % of patients with younger onset versus approximately 40 % in older onset diabetes.[1,2] More than 50 % of incorrectly treated patients lose several lines of visual acuity within a few years so needs a timely treatment.[3] DME has become a major public health problem due to the increasing incidence of type II diabetes in the working age population.[4]

The worldwide prevalence of diabetes mellitus in 2011 was approximately 366 million, estimated that the prevalence will reach 552 million people by 2030 (International Diabetes Federation 2011).[5] Diabetic macular oedema causes acquired visual loss in approximately 6.8 % of people with diabetes (Antonetti 2012;[6] Bunce 2008;[7] Moss 1998;[8] Yau 2012.[9] The prevalence of DME in mild non-proliferative retinopathy is 3 %, in moderate-to-severe non-proliferative retinopathy prevalence rises to 38 % and increasing to 71 % in eyes with proliferative retinopathy.[10]

The pathogenesis of DME is multifactorial. Any changes in cellular junctions, loss of pericytes and endothelial cells, dilation of retinal vessels, leukostasis and vitreoretinal traction, causes the alteration of blood-retinal barrier.[11,2] The alteration of blood-retinal barrier is generally due to the increase in inflammatory mediators like prostaglandins, specific pro-inflammatory interleukins and angiogenic substances such as vascular endothelial growth factors (VEGF).[12] Normal retinal pigmented epithelial cells secrete VEGF in the condition of hypoxia.[12,13] VEGF is a homodimeric protein which acts by inducing an increase in vascular permeability by stimulating the proliferation of vascular endothelial cells.[11] Increase in vascular permeability results in leakage of fluid and plasma constituents into the retina leading to DME. Thus, inhibition of VEGF may provide an alternative therapeutic approach in DME.

For refractory DME, Grid laser treatment has been the gold standard, but it has been replaced almost completely by pharmacologic treatments, such as intravitreal steroids or anti-VEGF.[14,15] Laser photocoagulation of the macular region and pars-plana vitrectomy greatly reduce the chance of visual loss from macular oedema, but usually does not cause improvement of visual acuity, however these procedures are associated with significant side-effects and complications.[15]

Recent multicentre randomized clinical trials have demonstrated that intravitreal injections of steroids or anti-VEGF molecules result in significant improvement of visual acuity, and help the patient not to progress towards more advanced forms of diabetic retinopathy.[16,17]

Ranibizumab (anti- VEGF) is a fully humanised monoclonal antibody fragment (Fab) which binds to multiple variants of VEGF-A.[18] It is an effective treatment for DME, causes significant improvement in BCVA and in anatomic outcomes.[19]

Triamcinolone acetonide (corticosteroid) act by regulating endothelial cell tight junctions by inhibiting VEGF, cytokines and growth factors. It causes local reduction of inflammatory mediators by inhibiting prostaglandin and leukotriene synthesis. The resultant anti-inflammatory effect contributes to the reduction of macular edema.[20] Increased diffusion by modulation of calcium channels also improves the efficacy of corticosteroids in reducing macular edema.[21]

Aim of the Study

Comparison of efficacy and safety of intravitreal injection Ranibizumab and Triamcinolone acetonide in diabetic macular edema.

METHODS

This is a prospective randomized study including 42 eyes in 42 patients' ≥ 18 years of age, both type 1 and type 2 diabetic people with non tractional diabetic macular edema presenting to outpatient department in our tertiary care centre of Gorakhpur UP, from November 2019 – December 2020.

Patients with any active ocular infection, uncontrolled glaucoma (IOP ≥ 25 mmHg) at the time of screening or within 6 months before the baseline visit, neovascular glaucoma or neovascularization of the iris, macular ischemia, anti-VEGF injection within 3 months before screening, intraocular / periocular / subtenon corticosteroids within 3 months before screening, any corticosteroid implants in the study eye, previous pan-retinal, focal or grid laser photocoagulation, history of stroke, uncontrolled blood pressure (systolic value of > 150 mmHg or diastolic value of > 90 mmHg) at the screening were excluded from this study.

Examination

- An informed consent was taken from all the patients participating in the study.
- Visual acuity assessment by Snellen chart.
- Intraocular pressure (IOP) by tonometry.
- Slit lamp examination for anterior segment.
- Direct and Indirect ophthalmoscopy for Fundus examination.
- Spectral Domain Optical Coherence Tomography (SD - OCT) for foveal and para-foveal thickness.
- Fundus fluorescein angiography.

OCT was performed before intravitreal injection (at baseline), at 2 week and at 4 week after the injection.

Technique of Injecting Intravitreal Injection

The injection was done in operation theatre with full aseptic precaution under topical anaesthesia by instilling 4 % lidocaine. 10 % povidone iodine applied on the lids and lashes. A sterile speculum was placed between the eyelids then 5 % povidone iodine instilled on the ocular surface 1 - 2 minutes before injection. Additional topical anaesthesia was achieved by 4 % lidocaine. Injection Ranibizumab (0.05 ml ; 0.50 mg) in an insulin syringe with a 30-gauze needle was injected through the pars plana route into the vitreous cavity through the sclera 4 mm posterior to the limbus at inferotemporal quadrant. With similar technique, injection

Triamcinolone acetonide (4 mg in 0.1 ml) injected intravitreally but with tuberculin syringe with 26 gauze needle. Post injection light perception and IOP was monitored. Topical antibiotics 4 times a day and topical timolol maleate 2 times a day were prescribed for 7 days post injection. Tablet acetazolamide 250 mg stat and oral antibiotic ofloxacin prescribed for 3 days.

Follow-up was done at 1st day, 1 week, 2 week and 4 week post-injection and OCT was done at 2 week and 4 week of follow-up.

Statistical Methodology

Numerical data were expressed as mean and standard deviation (Mean ± SD). Statistical analysis was done using SPSS software. $P \leq 0.05$ was considered as statistically significant. Student t- test was used to compare between the two treatment groups.

RESULTS

	Gender	No. of pt (n=42)	Percentage
Group A (Ranibizumab)	Male	12	57.14 %
	Female	9	42.85 %
Group B (Triamcinolone)	Male	10	47.61 %
	Female	11	52.38 %

Table 1. Gender Distribution

Improved BCVA	No. of pt at 2 wk post-inj	Percentage	No. of pt at 4 wk post-inj	Percentage
1 line	3	21 %	6	30 %
2 lines	2	14 %	2	10 %
3 lines	5	36 %	4	20 %
4 lines	3	21 %	5	35 %
5 lines	1	7 %	3	15 %

Table 2. Improvement in BCVA at 2 Week and 4 Week following Intravitreal Ranibizumab

Improved BCVA	No. of pt at 2 wk post-inj	Percentage	No. of pt at 4 wk post-inj	Percentage
1 line	4	22 %	2	11 %
2 lines	3	16.6 %	2	11 %
3 lines	5	27.7 %	4	22 %
4 lines	5	27.7 %	7	38.8 %
5 lines	1	5.5 %	3	16.6 %

Table 3. Improvement in BCVA at 2 Week and 4 Week following Intravitreal Triamcinolone Acetonide

Foveal and Para-Foveal Thickness	Treatment	Mean	Standard Deviation	P Value
Foveal thickness at baseline	Ranibizumab	510	80.13	P = 0.387
	Triamcinolone	536	110.24	
Para-foveal thickness at baseline	Ranibizumab	476	68.12	P = 0.403
	Triamcinolone	495	77.43	
Foveal thickness at 2 week	Ranibizumab	388	62.04	P = 0.035
	Triamcinolone	352	43.68	
Para-foveal thickness at 2 week	Ranibizumab	432	56.94	P = 0.043
	Triamcinolone	397	51.91	
Foveal thickness at 4 week	Ranibizumab	316	56. 84	P = 0.005
	Triamcinolone	276	27.10	
Para-foveal thickness at 4 week	Ranibizumab	346	60.47	P = 0.007
	Triamcinolone	306	23.29	

Table 4. Comparison in both Study Groups Regarding Foveal and Para-Foveal Thickness

Baseline Characteristics

Forty two subjects were enrolled in our study as per inclusion criteria. Patients were randomly divided into two groups. Group A treated with intravitreal ranibizumab, and Group B treated with intravitreal triamcinolone acetonide consisted of 21 eyes (male, 12 ; female, 9) and 21 eyes (male, 10; female, 11) in group A and B respectively. All 42 patients completed follow-up visit. The mean age of patients was 56.48 years in group A and 58.63 years in group B. None of them had received prior intravitreal ranibizumab or triamcinolone or laser photocoagulation. The baseline mean intraocular pressure value in group A and group B were 17.16 and 17.11 mmHg respectively. The baseline mean systolic and diastolic B.P value were 133.14 and 77.14 mmHg respectively in group A and 133.52 and 79.23 mmHg respectively in group B.

Visual Acuity Outcomes

In Group A

At the end of 2 week, 3 patients had improved visual acuity of 1 line, 2 patients 2 lines, 5 patients 3 lines, 3 patients 4 lines and 1 patient had 5 lines of improvement.

At the end of 4 week, 6 patients had improved visual acuity of 1 line, 2 patients 2 lines, 4 patients 3 lines, 5 patients 4 lines and 3 patients had 5 lines of improvement.

In Group B

At the end of 2 week, 4 patients had improved vision of 1 line, 3 patients 2 lines, 5 patients 3 lines, 5 patients 4 lines and 1 patient had 5 lines of improvement.

At the end of 4 week, 2 patients had improved vision of 1 line, 2 patients 2 lines, 4 patients 3 lines, 7 patients 4 lines and 3 patients had 5 lines of improvement.

Optical Coherence Tomography Outcomes

In group A, mean foveal thickness values at pre-injection, 2 week and 4 week after injection was 510 µm, 388 µm and 316 µm respectively and mean para-foveal thickness values at pre-injection, 2 week and 4 week after injection was 476 µm, 432 µm and 346 µm respectively.

In group B, mean foveal thickness values at pre-injection, 2 week and 4 week after injection was 536 µm, 352 µm and 276 µm respectively and mean para-foveal thickness values at pre-injection, 2 week and 4 week after injection was 495 µm, 397 µm and 306 µm respectively.

Safety

During the course of this study, there was no case of inflammation, ocular infection, decrease in visual acuity or vision loss, uveitis, ocular toxicity, retinal detachment, vitreous haemorrhage, cataract or endophthalmitis observed in both groups. No thromboembolic events like myocardial infarction, transient ischemic attacks, cerebrovascular accidents or peripheral vascular disease were reported during follow-up. Blood pressure was monitored regularly before injection and at each follow-up and there were no unusual rise in blood pressure in both groups.

IOP was stable in group A but not in group B, out of 21 patients 5 (23 %) had high IOP (25 - 35 mmHg) after injection, treated with IOP lowering medications.

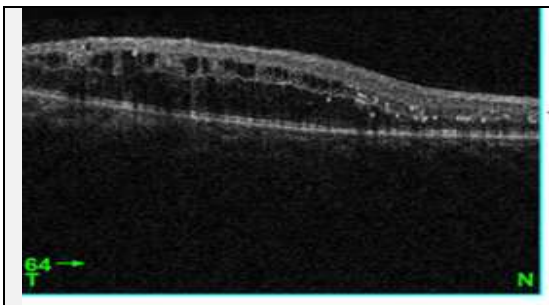

Figure 1a. OCT at Baseline before Injection Ranibizumab

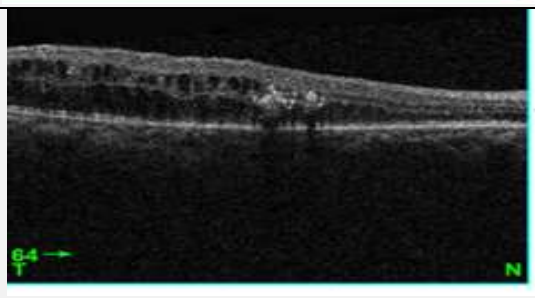

Figure 1b. OCT after 2 Week of Injection Ranibizumab

Figure 1c. OCT after 4 Week of Injection Ranibizumab

Figure 1. A Case Treated with Intravitreal Ranibizumab. OCT at Baseline, 2 Week and 4 Week after Injection

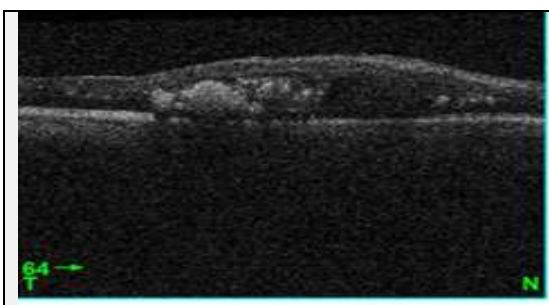

Figure 2a. OCT at Baseline before Injection Triamcinolone Acetonide

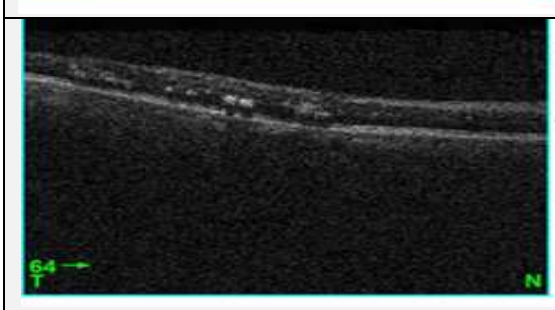

Figure 2b. OCT after 2 Week of Injection Triamcinolone Acetonide

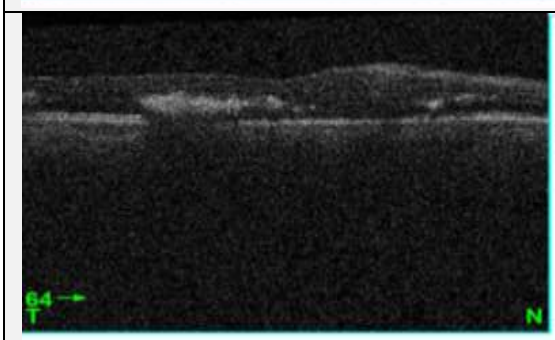

Figure 2c. OCT after 4 Week of Injection Triamcinolone Acetonide

Figure 2. A Case Treated with Intravitreal Triamcinolone Acetonide. OCT at Baseline, 2 Week and 4 Week after Injection

DISCUSSION

Visual Acuity

In our study, after intravitreal injection in both study groups, improvement in visual acuity were observed within 1 week and continued throughout 4 week.

In Group A

At the end of 2 week, 3 patients (21 %) had improved BCVA of 1 line, 2 patients (14 %) had improved 2 lines ,5 patients (36 %) had improved 3 lines, 3 patients (21 %) had improvement 4 lines and 1 patient (7 %) had improved 5 lines.

At the end of 4 week, 6 patients (30 %) had improved BCVA of 1 line, 2 patients (10 %) had improved 2 lines, 4 patients (20 %) had improved 3 lines, 5 patients (25 %) had improved 4 lines and 3 patients (15 %) had improved 5 lines.

In Group B

4 patients (22 %) had improved BCVA of 1 line, 3 patients (16.6 %) had improved 2 lines, 5 patients (27.7 %) had improved 3 lines, 5 patients (27.7 %) had improved 4 lines and 1 patient (5.5 %) had improved 5 lines at 2 week after injection. At the end of 4 week, 2 patients (11 %) had improved BCVA of 1 line, 2 patients (11 %) had improved 2 lines, 4 patients (22 %) had improved 3 lines, 7 patients (38.8 %) had improved 4 lines and 3 patients (16.6 %) had improved 5 lines. A study conducted by Deepti et al[22] reported that improvement of best corrected visual acuity 1-2 snellen lines at 3 months of follow-up period after receiving 4 mg intravitreal triamcinolone acetonide in patients with diabetic macular edema.

Intraocular Pressure

During the course of our study, IOP was stable in all patients in ranibizumab treated group. In triamcinolone treated group 5 patients (23 %) showed raised IOP to > 25 mmHg after injection, required to treat with anti-glaucoma medications to lower IOP. Sikander A. K. Lodhi et al.[23] concluded in their study that on comparison between 4-mg and 1-mg sub-group, incidence of adverse effects were high in the 4 - mg sub-group of intravitreal triamcinolone. Incidence of increased IOP ≥ 5 mmHg from baseline was more in patients in 4-mg sub-group and incidence of lenticular changes was also more reported in 4 - mg group than in 1 - mg group.

Foveal and Para-Foveal Thickness Post Injection in both Study Groups

At Baseline

Mean foveal thickness in group A and group B was 510 ± 80.13 µm and 536 ± 110.24 µm respectively and mean para-foveal thickness in group A and group B was 476 ± 68.12 µm and 495 ± 77.43 µm respectively.

At 2 Week

Mean foveal thickness in group A and group B was 388 ± 62.04 µm and 352 ± 43.68 µm respectively (p = 0.0357) and mean para-foveal thickness in group A and group B was 432 ± 56.94 µm and 397 ± 51.91 µm respectively (p = 0.0438)

At 4 Week

Mean foveal thickness in group A and group B was 316 ± 56.84 µm and 276 ± 27.10 µm respectively (p = 0.0059) and mean para-foveal thickness in group A and group B was 346 ± 60.47 µm and 306 ± 23.29 µm respectively (p = 0.0073).

Thus a comparison between both study groups showed statistically significant decrease in mean foveal thickness at 2 week (P = 0.0357) and at 4 week (P = 0.0059) and statistically significant decrease in mean para-foveal thickness at 2 week (P = 0.0438) and at 4 week (P = 0.0073).

A comparative study conducted by Mansour Hassan Ahmed et al[24] between intravitreal Ranibizumab and Triamcinolone in treatment of diabetic macular edema, concluded that ranibizumab treated group showed a statistically significant difference in mean central macular thickness at one, three and six months (p = 0.010), (p < 0.001) and (p < 0.001) respectively and a statistically significant difference was observed at one, three and six months (p < 0.001), (p < 0.001) and (p = 0.025) respectively in triamcinolone treated group also. His study suggested that ranibizumab treated group showed significant improvement in the mean BCVA at three months (p = 0.003) and six months (p = 0.001) and triamcinolone treated group showed significant improvement at one (p < 0.001), three months (p < 0.001) and six months (p = 0.015). His conclusion was that comparison between the two study groups revealed statistical significant difference at one and three months (p < 0.001) but no significant difference at six months.

A study conducted by Pichandi Kiruba Shankari et al[25] concluded that ranibizumab therapy 0.5 mg / 0.05 ml showed statistically significant improvement in visual acuity and reduction of central foveal thickness in comparison to triamcinolone acetonide 4 mg / 0.1 ml therapy. Oh et al.[26] reported that reduction in central macular thickness was maintained for 3 months after intravitreal triamcinolone but in the intravitreal bevacizumab group, reduction in central macular thickness persisted for two months after injection. Another study by Paccola et al.[27] suggested that a single injection of intravitreal triamcinolone significantly reduce the central macular thickness compared with one intravitreal bevacizumab during an eight-week period in patient with diabetic macular oedema. Mohsen A. Abou Shousha et al[28] compared the results of intravitreal Ranibizumab at 1 week and 1 month in diabetic macular oedema with conclusion that the improvement in best corrected visual acuity at baseline and at 1 week after injection was statistically significant (p = 0.012) but not statistically significant (p = 0.361) at 1 week and at 1 month. Regarding the difference between the central macular thickness at baseline and at 1 week after injection was statistically significant (p = 0.025) but the difference between the central macular thickness of the eyes at 1 week and at 1 month after injection was not statistically significant (p = 0.816) in his result.

Another study conducted by Yoshiro Minami et al[29] on short- term effects of intravitreal ranibizumab therapy on diabetic macular oedema suggested that the decrease in mean foveal thickness after 2 hour of injecting intravitreal ranibizumab was significantly (P = 0.01) correlated with the decrease in mean foveal thickness after one month and the decrease in mean foveal thickness was paralleled with improvement in mean visual acuity after 1 month.

Nicholson BP et al[30] analysed that intravitreal ranibizumab safely reduces the risk factors of diabetic retinopathy and more feasible when compared to intravitreal triamcinolone acetonide because intravitreal triamcinolone can cause various adverse effects such as glaucoma, cataract or even endophthalmitis whereas intravitreal ranibizumab showed short term benefits during the treatment with naïve eyes. Many researchers also reported complications such as glaucoma,[31,32] cataract,[31,32] endophthalmitis,[33] and pseudoendophthalmitis[34] after intravitreal triamcinolone acetonide injection. Darius M Moshfeghi et al[35] reported an incidence of endophthalmitis 0.87 % in patients with DME after receiving intravitreal triamcinolone acetonide during 6 week follow-up period. The median time to presentation was 7.5 days (range 1 - 15 days) after intravitreal triamcinolone.

CONCLUSIONS

Intravitreal injection Ranibizumab and Triamcinolone acetonide are equally effective to lower foveal and para-foveal thickness and to improve BCVA but in Triamcinolone treated group, IOP raised in few patients, anti-glaucoma medications were advised in these patients to lower the IOP. Thus, intravitreal Ranibizumab injection 0.50 mg in 0.05 ml is effective, safe and well tolerated in reducing foveal and para-foveal thickness, improving best corrected visual acuity in patients with diabetic macular oedema.

Limitations of the Study

The main shortcoming of this study is that less number of patients was included in our study and there are very limited follow-up period. Due to short period of this study, long term adverse effects of the study drugs cannot be assessed and recurrence of the disease cannot be mentioned.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Cunha-Vaz J, de Abreu JRF, et al. Early breakdown of the blood-retinal barrier in diabetes. Br J Ophthalmol 1975;59(11):649-656.
[2] Ehrlich R, Harris A, Ciulla TA, et al. Diabetic macular edema: physical, physiological and molecular factors contribute to this pathological process. Acta Ophthalmol 2010;88(3):279-291.
[3] Ferris FL 3rd, Patz A. Macular edema. A complication of diabetic retinopathy. Surv Ophthalmol 1984;Suppl 28:452-461.
[4] Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2014;14(6865):782-787.
[5] International Diabetes Federation. Diabetes Atlas. 5th edn. Brussels: International Diabetes Federation, 2011.
[6] Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. New England Journal of Medicine 2012;366(13):1227-1239.
[7] Bunce C, Wormald R. Causes of blind certifications in England and Wales: April 1999 - March 2000. Eye 2008;22(7):905-911.
[8] Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. Ophthalmology 1998;105(6):998-1003.
[9] Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of Diabetic retinopathy. Diabetes Care 2012;35(3):556-564.
[10] Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91(12):1464-1474.
[11] Bhagat N, Grigorian RA, Tutela A, et al. Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol 2009;54(1):1-32.
[12] Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331(22):1480-1487.
[13] Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am J Ophthalmol 1994;118(4):445-450.
[14] Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med 2012;366(13):1227-1239.
[15] Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 1. Arch Ophthalmol 1985;103(12):1796-1806.
[16] Nourinia R, Soheilian M. State of the art management of diabetic macular edema. World J Ophthalmol 2015;5(2):55-72.
[17] Bandello F, Cunha-Vaz J, Chong NV, et al. New approaches for the treatment of diabetic macular edema: recommendations by an expert panel. Eye (Lond) 2012;26(4):485-493.
[18] Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26(8):859-870.
[19] Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112(10):1747-1757.

[20] Hood PP, Cotter TP, Costello JF, et al. Effect of intravenous corticosteroid on ex vivo leukotriene generation by blood leukocytes of normal and asthmatic patients. Thorax 1999:54(12):1075-1082.
[21] Sze PY, Iqbal Z. Glucocorticoid actions on synaptic plasma membranes: modulation of I^{125} calmodulin binding. J Steroid Biochem Mol Biol 1994;48(2-3):179-186.
[22] Deepti K, Kailwoo SK. Visual acuity after intravitreal injection of triamcinolone acetonide in patients with diabetic macular edema. International Journal of Biomedical Research 2016;7(3):115-117.
[23] Lodhi SAK, Reddy S, Devulapally S. Intravitreal triamcinolone in diabetic macular edema: a comparative study of 1mg and 4mg doses. J Evolution of Medical and Dental Sciences 2015;4(53):9191-9201.
[24] Ahmed MS, El-Khalek MOA, Dabees MMF, et al. Comparative study between intravitreal ranibizumab and triamcinolone treatment of diabetic macular edema as regard to optical coherence tomography changes and visual acuity. Rev Bras Oftalmol 2019;78(4):219-226.
[25] Shankari PK, Johny ME, Suresh S, et al. Comparative study of intravitreal ranibizumab injection and intravitreal triamcinolone injection in diabetic macular edema. Drug Invention Today 2020;14(3):399-404.
[26] Oh SB, Moon JW, Kim HC. Comparison of effects of intravitreal triamcinolone and bevacizumab in the treatment of diabetic macular edema. J Korean Ophthalmol Soc 2009;50(8):1190-1196.
[27] Paccola L, Costa RA, Folgosa MS, et al. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). Br J Ophthalmol 2008;92(1):76-80.
[28] Shousha MAA. Comparison between 1-week and 1-month results of intravitreal ranibizumab in diabetic macular edema. J The Egypt Ophthalmol Soc 2015;108(4):249-254.
[29] Minami Y, Nagaoka T, Ishibazawa A, et al. Short-term effects of intravitreal ranibizumab therapy on diabetic macular edema. BMC Ophthalmol 2017;17(1):28.
[30] Nicholson BP, Schachat AP. A review of clinical trials of anti-VEGF agents for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 2010;248(7):915-930.
[31] Jonas JB, Kreissig I, Sofker A, et al. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol 2003;121(1):57-61.
[32] Jonas JB, Kreissig I, Hugger P, et al. Intravitreal triamcinolone acetonide for exudative age related macular degeneration. Br J Ophthalmol 2003;87(4):462-468.
[33] Moshfeghi DM, Kaiser PK, Scott IU, et al. Acute endophthalmitis following intravitreal triamcinolone acetonide injection. Am J Ophthalmol 2003;136(5):791-796.
[34] Sutter FK, Gillies MC. Pseudo-endophthalmitis after intravitreal injection of triamcinolone. Br J Ophthalmol 2003;87(8):972-974.
[35] Moshfeghi DM, Kaiser PK, Scott IU, et al. Acute endophthalmitis following intravitreal triamcinolone acetonide injection. Am J Ophthalmol 2003;136(5):791-796.