Original Article

Effect of Ranibizumab Injections on Visual Acuity and Central Macula Thickness

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ABSTRACT

Purpose: To see the effect of Ranibizumab at 1-monthly and 2-monthly intervals on visual acuity and central macula thickness among patients with diabetic macular edema, neovascular age-related macular degeneration and diabetic retinopathy.

Study Design: Retrospective review of clinical record.

Place and Duration of Study: The present study was conducted at four eye centers (Al-Shami Eye Center, Sudan Eye Center, Makkah Eye Complex and Nor-Aloyon Eye Hospital) located at Khartoum state of Sudan from January 2021 and June 2021.

Methods: A total of 109 records of patients with diabetic retinopathy, age related macular degeneration and macular edema were included. They were categorized into 4 groups; group A (wet age-related macular edema (WAMD, n = 16)), group B (macular edema (ME, n = 32)), group C (proliferative diabetic retinopathy (PDR, n = 31)), and group D (non-proliferative diabetic retinopathy and macular edema (NPDR + ME, n = 30)). All participants underwent full ophthalmic examination before the injection, at one month and two months after the injection. Means, standard deviations and frequencies were calculated. ANOVA was used to find any significant difference between the study groups and the impact of treatment.

Results: Mean age of patients was 57.73 ± 10.44 years. There was significant improvement in terms of mean visual acuity from baseline to third follow up in all study groups, ($F(1, 105) = 14.94$, $P < 0.001$), with no significant differences in this improvement between the study groups, $F(1.83, 5.48) = 14.6$, $P = 0.19$.

Conclusion: Use of Lucentis has demonstrated a statistically significant reduction in CMT and improvement in BCVA. However, none of the patients showed a complete resolution of edema at the end of last follow up.

Key Words: Diabetic retinopathy; Macular edema; Ranibizumab; Sudan.

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INTRODUCTION

Neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) are major causes of visual impairment in the elderly population.[1] Diabetic macular edema (DME) is a common manifestation of diabetic retinopathy (DR), which is one of the leading causes of vision impairment in untreated diabetic patients.[2] The increased incidence of DM is causing a rise in total number of patients with DR worldwide. However, recent developments in drugs are reducing the prevalence of vision loss caused by these diseases.[3-5] AMD affects individuals aged 50 years and older leading to irreversible severe impairment of central vision (blindness).

Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) has been shown to reduce edema, improve vision and prevent further visual loss in patients with DME, which have replaced laser photocoagulation as the standard of care for people with DME.[6,7] There are many anti-anti-VEGF drugs used for the treatment of retinal diseases.[8-12]

Two monthly injections of Ranibizumab, while not significantly increasing vision, may have a role in preventing visual loss. A multicenter, randomized study reported that patients treated with a Ranibizumab treat and extend protocol (T&E) which required few injections.[13] Furthermore, a retrospective, observational study confirmed that Ranibizumab used according to T&E protocol yielded a stronger improvement in log MAR visual acuity as compared to the pro re nata (PRN) protocol which required longer treatment.[14]

Most of the data available on the use of Ranibizumab are derived from developed countries. Very little data are available from developing countries, especially those in Africa, where the population is more interested in traditional medicine.[15] The current study aimed to assess the effect of Lucentis (Genentech/Roche), the available brand of Ranibizumab in Sudan, on visual acuity and central macula thickness among patients with neovascular (wet) age-related macular degeneration, macular edema, and diabetic retinopathy.

METHODS

The present study was conducted at four eye centers (Al-Shami Eye Center, Sudan Eye Center, Makkah Eye Complex and Nor-Aloyon Eye Hospital) located at Khartoum state of Sudan from January 2021 and June 2021. Patients with diabetic retinopathy, age related macular degeneration and macular edema were included. Subjects with other ocular conditions that expected to interfere with the results of the study were excluded. Ethical approval was obtained from the Review Boards of the four ophthalmic centers and the study was done in accordance with the tenets of the Declaration of Helsinki.

A total of 109 records that met the inclusion criteria of the study were included in the study. Patients were categorized into 4 groups according to diagnosis; group A (wet age-related macular edema (WAMD, n = 16)), group B (macular edema (ME, n = 32)), group C (proliferative diabetic retinopathy (PDR, n = 31)), and group D (non-proliferative diabetic retinopathy and macular edema (NPDR + ME, n = 30)).

All participants underwent full ophthalmic examination before the injection, at one month and two months after the injection. Examination results included in this study were uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) which was evaluated using a chart projector (Towa 1698-2 Nakano-shin Nagano 383-0013, Japan), objective refraction (spherical equivalent of refraction, SER) measured using an auto refracto-keratometer (Topcon. Auto-Kerato-Refractometer, Japan. KR-8900) and central macular thickness (CMT) using optical coherence tomography (OCT Advance Nidek RS-3000; Nidek Co. Ltd., Gamagori, Japan).

Data were analyzed using the SPSS software for Windows version 25 (IBM Corporation, Armonk, NY, USA). Means, standard deviations and frequencies were used to describe the demographic and clinical profile of subjects. One way between groups ANOVA was used to find any significant difference between the study groups and two-way repeated measures ANOVA was used to evaluate the impact of the treatment over the time and within different study groups. P value of less than 0.05 was considered statistically significant.

RESULTS

Data from records of 109 patients treated by Lucentis injection were analyzed. Sixteen patients (14.68%) had wet age-related macular edema (WAMD) categorized as group **A**, 32 subject (29.36%) had macular edema

Table 1: *Age and gender distribution of different study groups.*

Group	Age (Mean ± SD)	Gender	
		Male (%)	Female (%)
A (WAMD) n = 16	61.38 ± 7.93	9 (65.25%)	7 (43.75%)
B (ME) n = 32	55.38 ± 10.75	20 (62.5%)	12 (37.5%)
C (PDR) n = 31	58.97 ± 9.88	15 (48.4%)	16 (51.6%)
D (NPDR + ME) n = 30	57.03 ± 11.54	13 (43.4%)	17 (56.6%)
Total (n = 109)	57.73 ± 10.44	57 (52.3%)	52 (47.7%)

SD = Standard deviation, n = Number,
WAMD = Wet age-related macular edema,
ME = Macular edema, PDR = Proliferative diabetic retinopathy,
NPDR = Non-proliferative diabetic retinopathy

Table 2: *Mean ± SD of all clinical parameters at baseline, one month post the first injection and two months post the second injection according to different study groups.*

Group	Baseline				One Month				Two Months			
	UCVA	BCVA	SE (D)	CMT (µm)	UCVA	BCVA	SE (D)	CMT (µm)	UCVA	BCVA	SE (D)	CMT (µm)
A (WAMD)	0.12 ±	0.18 ±	0.71 ±	401.50 ±	0.12 ±	0.18 ±	0.60 ±	347.44 ±	0.13 ±	0.18 ±	0.29 ±	371.75 ±
n = 6	0.06	0.14	2.77	142.41	0.07	0.12	0.27	132.39	0.06	0.13	2.59	124.54
B (ME)	0.24 ±	0.35 ±	1.82 ±	454.91 ±	0.26 ±	0.36 ±	1.38 ±	422.31 ±	0.27 ±	0.39 ±	1.48 ±	385.93 ±
n = 2	0.24	0.32	2.76	147.33	0.24	0.31	2.73	140.21	0.21	0.32	2.69	136.56
C (PDR)	0.17 ±	0.33 ±	2.33 ±	425.97 ±	0.24 ±	0.42 ±	2.1 0±	345.48 ±	0.25 ±	0.45 ±	0.70 ±	336.58 ±
n =31	0.14	0.32	1.48	177.88	0.18	0.35	1.27	122.34	0.19	0.36	1.51	116.81
D (NPDR +	0.28 ±	0.41 ±	1.48 ±	466.53 ±	0.29 ±	0.43 ±	1.35 ±	410.77 ±	0.32 ±	0.45 ±	1.35 ±	400.77 ±
ME) n =30	0.25	0.33	2.17	120.87	0.24	0.32	1.96	112.86	0.24	0.33	1.61	103.39
Total	0.21 ±	0.34 ±	1.71 ±	466.04 ±	0.24 ±	0.37 ±	1.46 ±	390.26 ±	0.26 ±	0.39 ±	1.05 ±	373.89 ±
n = 109	0.21	0.31	2.32	149.31	0.21	0.31	2.20	129.19	0.21	0.33	2.13	121.70

SD = Standard deviation, n = Number, WAMD = Wet age-related macular edema, ME = Macular edema, PDR = Proliferative diabetic retinopathy, NPDR = Non-proliferative diabetic retinopathy, UCVA = Uncorrected visual acuity, BCVA = Best-corrected visual acuity, CMT = Central macula thickness

(ME) categorized as group **B**, 31 patients (28.44%) had proliferative diabetic retinopathy (PDR) categorized as group **C** and 30 patients (27.52%) had non-proliferative diabetic retinopathy and macular edema (NPDR + ME) categorized as group **D**.

As shown in table 1, mean age of all patients was 57.73 ± 10.44 (range; 30 to 85 years), which was 61.38 ± 7.93, 55.38 ± 10.75, 58.97 ± 9.88 and 57.03 ± 11.54 for group A, B, C and D, respectively. There were 57 males (52.3%) and 52 females (47.7%).

Mean uncorrected visual acuity (UCVA) for the total patients at baseline (before injection) was 0.21 ± 0.20 (range; 0.00 to 1.0) and mean best corrected visual acuity was 0.34 ± 0.31 (range; 0.1 to 1.0). Mean baseline spherical equivalent of refraction was 1.71 ± 2.32 (range; -2.75 to 13.00 D). Table 2 illustrates mean ± SD of all clinical parameters at baseline, one-month post-first injection and two months post-second injection according to the different study groups.

Normality of data, homogeneity of variance and dependency were tested. One-way analysis of variance (ANOVA) was used to identify differences between the study groups in term of patients' age. No statistically significant differences were found between the four groups F (3) = 1.39, P = 0.25. In the baseline data, the same test indicated no significant differences in terms of BCVA (F (3) = 2.02, P = 0.12), SER (F (3) = 1.91, P = 0.13) and CMT (F (3) = 0.86, P = 0.47) between the study groups. However, significant mean difference was detected only in term of UCVA (F (3) = 2.83, P = 0.04).

Two-way repeated measures ANOVA was used to investigate the impact of Lucentis treatment over the time within different variables studied as well as within the different groups of the study. Change in UCVA over time is shown in figure 1. There was significant improvement in terms of mean UCVA from baseline to the third follow up session in all study groups, (F (1, 105) =14.94, P < 0.001), with no significant differences in this improvement between the study groups, F (1.83, 5.48) =14.6, P = 0.19.

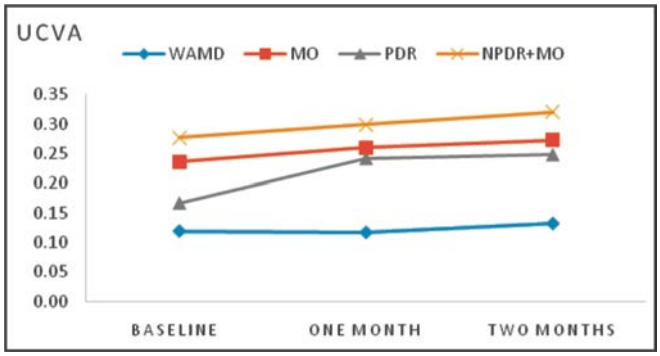

Figure 1: Change in uncorrected visual acuity (UCVA) after Lucentis injection.
WAMD = Wet age-related macular edema, ME = Macular edema, PDR = Proliferative diabetic retinopathy, NPDR = Non-proliferative diabetic retinopathy.

Figure 2 depicts changes in BCVA over time for the four patients' groups. Two-way repeated measures ANOVA indicated that BCVA significantly improved over the time after Lucentis injection in the four study groups (F (1.69, 5.09) = 4.14, P = 0.017) with no significant difference in this improvement between the study groups, F (1, 3) = 1.21, P = 0.31.

Figure 3 shows changes in CMT over time for the

four patients' groups. The two-way analysis of variance also indicated the effect of Lucentis injection over time in reducing the mean CMT in all the study groups, F (1.31, 3.92) = 19.41, P < 0.001. However, there was no significant difference between the four groups in term of CMT reduction across the time, F (1.31, 3.92) = 1.01, P =0.40.

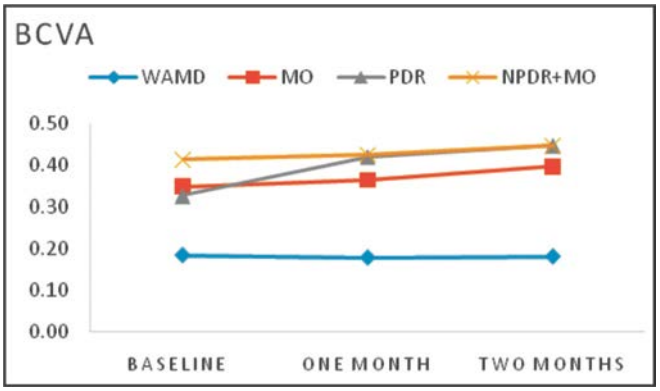

Figure 2: Change in best-corrected visual acuity (BCVA) after Lucentis injection.
WAMD = Wet age-related macular edema, ME = Macular edema, PDR = Proliferative diabetic retinopathy, NPDR = Non-proliferative diabetic retinopathy.

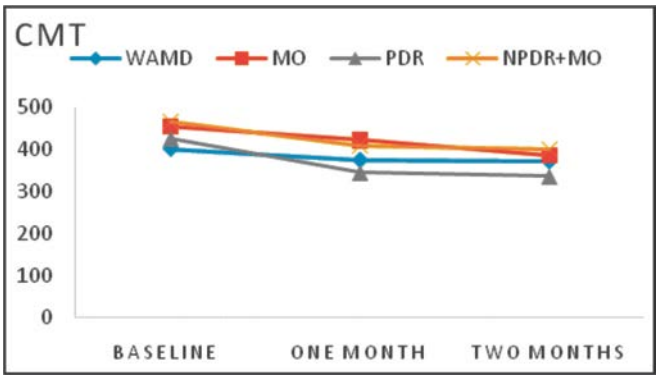

Figure 3: Change in central macula thickness (CMT) after Lucentis injection.
WAMD = Wet age-related macular edema, ME = Macular edema, PDR = Proliferative diabetic retinopathy, NPDR = Non-proliferative diabetic retinopathy.

DISCUSSION

Diabetes and its associated diseases such as diabetic retinopathy have a high economic burden in addition to the burden of health complications in African countries, including Sudan.[16] Consequently, diabetic macular edema and diabetic retinopathy have a negative impact on visual functions and quality of life of patients.[17] This is of concern to Sudan and other neighboring countries since diabetic retinopathy is known to be more prevalent in certain ethnicities such as Africans.[18] This study aimed to assess the effectiveness of a regimen of 3 doses of Ranibizumab injections (Lucentis, Genentech/Roche) administered to patients in tertiary eye care centers in Sudan.

Laser photocoagulation has been the standard treatment for DME and PDR for several decades to delay or prevent vision loss, however important improvement in visual acuity was uncommon.[19] The development of vascular endothelial growth factor (VEGF) inhibitory drugs, such as Ranibizumab, have helped in improvement of visual acuity, reduction in edema in DME and PDR and prevention of vision loss by neovascularization due to wet AMD.[20-22]

The patients included in this retrospective study had an average age of 57.73 ± 10.44 which is relatively younger than other studies that investigated the effect of Ranibizumab on visual acuity and central macula thickness.[14,22] The young age of patients seeking Lucentis treatment is in agreement with a previous study conducted in Sudan about the prevalence of diabetic retinopathy among diabetic patients attending a tertiary care center in Khartoum, Sudan.[23] The Lucentis regimen followed in this study was 3 injections that were administered in the first visit (baseline), after 1 month, then after 2 months. For DR and DME, Ranibizumab injections are administered under two main protocols; the pro re nata protocol (PRN) and the treat and extend protocol (T&E). However, due to financial restraints or physicians' references, the follow-up treatments beyond the 3 monthly loading doses vary between countries and among hospitals.[14, 24] On the other hand, management of neovascular (wet) age-related macular degeneration has no standard regimen, except for the 3 doses administered at baseline, 1 month and 2 months.[25] Thus, the Lucentis regimen followed in this study is identical to what is done for WAMD, and similar to the initial loading injections regimen followed in various hospitals around the world. It was seen in another study that treatment for DME with no less than three monthly Ranibizumab loading injections, with or without other supplementary treatments, was effective at 12 months thereafter.[24]

All the patients were assessed with the same equipment by the same practitioner and received the same Lucentis injection regimen by the same physician which ensured no inter-user variability or variations due to differences between instruments. All

patients showed a statistically significant increase in both UCVA and BCVA 2-months after intervention. This is in agreement with studies published in other countries such as Taiwan[24] and Switzerland.[14] However; data on BCVA beyond 2-month injection were not available in the patient's records included in the current study, whereas data obtained from other countries are available even beyond 12 months from baseline. Long-term evidence on use of Lucentis have demonstrated an improvement and stabilization of visual acuity.[14,20] We did not have data beyond 2 – months post injection which was caused by loss of follow up.

Use of Lucentis has demonstrated a statistically significant reduction in CMT. However, none of the patients showed a complete resolution of edema (a CMT below 300 µm). Very few patients usually reach the level of edema resolution. This is important because a rebound in thickness has been observed after six months of receiving treatment.[24] It is of interest to follow-up on the patients who received Lucentis treatment and investigate the rate of rebound of CMT.

A limitation of this study is its retrospective nature, which lacked data on visual acuity or central macula thickness after the 2 – month injection. This is partly due to the lack of compliance to follow-up appointments or due to the financial constrains that limit the access to reinjections. Thus, awareness of the need of follow-up is required. There is also a need for training of practitioners on follow-up of cases. National Health Service system that would offer Ranibizumab without cost or at a subsidized rate would encourage patients to follow-up on treatments regimen which would ensure better long term outcomes. Follow-up data after one year of receiving the 3 injections would allow for better comparison with the re-injections protocol followed in other countries. This will highlight the effectiveness of this 3-injections regimen, in addition to its subsequent affordability for low-income countries such as Sudan, and increased compliance due to reduced injection load.

CONCLUSION

Use of Lucentis has demonstrated a statistically significant reduction in CMT and improvement in BCVA. However, none of the patients showed a complete resolution of edema at the end of last follow up.

Conflict of Interest

Authors declared no conflict of interest.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board **(KBMA/1/2023).**

REFERENCES

1. **Borchers AT, Uibo R, Gershwin ME.** The geoepidemiology of type 1 diabetes. Autoimmun Rev. 2010; **9:** A355–365. Doi: 10.1016/j.autrev.2009.12.003
2. **Alwakeel JS, Sulimani R, Al-Asaad H, Al-Harbi A, Tarif N, Al-Suwaida A, et al.** Diabetes complications in 1952 type 2 diabetes mellitus patients managed in a single institution in Saudi Arabia. Ann Saudi Med. 2008; **28:** 260–266. Doi: 10.5144/0256-4947.2008.260
3. **Fong AH, Lai TY.** Long-term effectiveness of Ranibizumab for age-related macular degeneration and diabetic macular edema. Clin Interv aging, 2013; **8:** 467-483. Doi: 10.2147/CIA.S36811
4. **Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS.** Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane database Syst rev. 2014; **8 (8):** CD005139. Doi: 10.1002/14651858.CD005139.pub3
5. Stewart MW. A review of Ranibizumab for the treatment of diabetic retinopathy. Ophthalmol Ther. 2017; 6 (1): 33-47. Doi: 10.1007%2Fs40123-017-0083-9
6. **Mitchell P, Sheidow TG, Farah ME, Mahmood S, Minnella AM, Eter N, et al.** Effectiveness and safety of Ranibizumab 0.5 mg in treatment-naïve patients with diabetic macular edema: Results from the real-world global LUMINOUS study. Plos one, 2020; **15 (6):** e0233595. Doi: 10.1371/journal.pone.0233595
7. **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; **6 (6):** CD007419.
   Doi: 10.1002/14651858.cd007419.pub5
8. **Sarwar S, Clearfield E, Soliman MK, Sadiq MA, Baldwin AJ, Hanout M, et al.** Aflibercept for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2016; **(2) 2:** CD011346. Doi: 10.1002/14651858.cd011346.pub2
9. **Formoso G, Marata AM, Magrini N, Bero L.** A clearer view of evidence in treating macular degeneration: off-label policies and independent research. Cochrane Database Syst Rev. 2014; **(9):** D000090. Doi: 10.1002/14651858.ED000090.

10. **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 (4):** 185-222. Doi: 10.1159/000458539
11. **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 (6):** 636-643. Doi: 10.1097/icu.0000000000000424
12. **Bressler NM, Odia I, Maguire M, Glassman AR, Jampol LM, MacCumber MW, et al.** Association between change in visual acuity and change in central subfield thickness during treatment of diabetic macular edema in participants randomized to aflibercept, bevacizumab, or Ranibizumab: a post hoc analysis of the protocol T randomized clinical trial. JAMA Ophthalmol. 2019; **137 (9):** 977-985. Doi: 10.1001/jamaophthalmol.2019.1963
13. **Guymer RH, Markey CM, McAllister IL, Gillies MC, aHunyor AP, Arnold JJ, et al.** Tolerating subretinal fluid in neovascular age-related macular degeneration treated with Ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. Ophthalmology 2019; **126.5:** 723-734. Doi: 10.1016/j.ophtha.2018.11.025
14. **Augsburger M, Sarra GM, Imesch P.** Treat and extend versus pro re nata regimens of Ranibizumab and aflibercept in neovascular age-related macular degeneration: a comparative study. Graefe's Arch Clin Exp Ophthalmol. 2019; **257.9:** 1889-1895. Doi: 10.1007/s00417-019-04404-0
15. **Oyebode O, Kandala NB, Chilton PJ, Lilford RJ.** Use of traditional medicine in middle-income countries: a WHO-SAGE study. Health policy plan, 2016; **31 (8):** 984–991. Doi: 10.1093/heapol/czw022
16. **Mapa-Tassou C, Katte JC, Mba Maadjhou C, Mbanya JC.** Economic Impact of Diabetes in Africa. Current diabetes reports, 2019; **19 (2):** 5. Doi: 10.1007/s11892-019-1124-7
17. **Cooper O, Taylor DJ, Crabb DP, Sim DA, McBain H.** Psychological, social and everyday visual impact of diabetic macular oedema and diabetic retinopathy: a systematic review. Diabet Med. 2020; **37 (6):** 924–933. Doi: 10.1111/dme.14125
18. **Sivaprasad S, Gupta B, Crosby-Nwaobi R, Evans J.** Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. Surv Ophthalmol. 2012; **57 (4):** 347–370. Doi: 10.1016/j.survophthal.2012.01.004
19. **Mansour SE, Browning DJ, Wong K, Flynn Jr HW, Bhavsar AR.** The evolving treatment of diabetic retinopathy. Clin Ophthalmol. 2020; **14:** 653-678. Doi: 10.2147/OPTH.S236637.
20. **Bhandari S, Nguyen V, Fraser-Bell S, Mehta H, Viola F, Baudin F, et al.** Ranibizumab or Aflibercept for diabetic macular edema: comparison of 1-year outcomes from the fight retinal blindness! Registry. Ophthalmology, 2020; **127.5:** 608-615. Doi:10.1016/j.ophtha.2019.11.018
21. **Gross JG, Glassman AR, Liu D, Sun JK, Antoszyk AN, Baker CW, et al.** Diabetic Retinopathy Clinical Research Network. Five-year outcomes of panretinal photocoagulation vs. intravitreous Ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA Ophthalmol. 2018; **136 (10):** 1138-1148. Doi: 10.1001/jamaophthalmol.2018.3255
22. **Gonzalez VH, Campbell J, Holekamp NM, Kiss S, Loewenstein A, Augustin AJ, et al.** Early and long-term responses to anti–vascular endothelial growth factor therapy in diabetic macular edema: analysis of protocol I data. Am J Ophthalmol. 2016; **172:** 72-79. Doi: 10.1016/j.ajo.2016.09.012
23. **Elwali ES, Almobarak AO, Hassan MA, Mahmoud AA, Awadalla H, Ahmed MH.** Frequency of diabetic retinopathy and associated risk factors in Khartoum, Sudan: population based study. Int J Ophthalmol. 2017; **10 (6):** 948-954. Doi:10.18240/ijo.2017.06.18
24. **Tsai MJ, Hsieh YT, Peng YJ.** Real-life experience of Ranibizumab for diabetic macular edema in Taiwan. Int Ophthalmol. 2019; **39 (7):** 1511-1522. Doi: 10.1007/s10792-018-0970-7
25. **Li E, Donati S, Lindsley KB, Krzystolik MG, Virgili G.** Treatment regimens for administration of anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2020; **5 (5):** CD012208. Doi:10.1002/14651858.CD012208.pub2

Authors' Designation and Contribution

Mustafa Abdu; Associate Professor: *Concepts, Design, Data acquisition, Data analysis, Manuscript preparation, Manuscript review.*

Yazan Gammoh; Associate Professor: *Design, Manuscript preparation, Manuscript editing, Manuscript review.*

Abd Elaziz Mohamed Elmadina; Assistant Professor: *Design, Data analysis, Manuscript preparation, Manuscript editing.*

Mohaned Hassab-Elrasoul; Optometrist: *Concepts, Data acquisition, Manuscript review.*