Int Ophthalmol (2019) 39:1575–1580
https://doi.org/10.1007/s10792-018-0977-0

ORIGINAL PAPER

Evaluation of the effect of combined intravitreal ranibizumab injection and sub-tenon steroid injection in the treatment of resistant diabetic macular edema

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Received: 5 December 2017 / Accepted: 17 June 2018 / Published online: 26 June 2018

Abstract
Purpose To compare sub-tenon steroid plus anti-VEGF injection with anti-VEGF injection solely in the treatment of resistant diabetic macular edema (DME).
Method Patients who exhibited insufficient anatomic [over 350 µm central macular thickness (CMT)] and less than 3 lines of visual gain at least six anti-VEGF injections, were randomly divided into two groups. In group I, the anti-VEGF injection was performed 10 days after the sub-tenon steroid injection [Triamcinolone acetonide (Sinakort-A®)]. And anti-VEGF was performed when needed during the follow-up period. In group II, treatment was continued with anti-VEGF only. All patients' visual acuity and CMT were followed up for 6 months.
Results The baseline BCVA in group I and group II was 0.51 ± 0.667 logMAR and 0.47 ± 0.60 logMAR, respectively ($p = 0.52$). In group I and II, at the end of 6-month follow-up, BCVA improved to 0.38 ± 0.60 logMAR ($p < 0.001$) and 0.43 ± 0.60 logMAR ($p = 0.20$), respectively. The baseline CMT in group I and group II was 494 ± 118.32 and 438.20 ± 90.99 µm, respectively ($p = 0.029$). In group I and II, at the end of 6 months, CMT decreased to 302.57 ± 69.89 µm ($p < 0.001$) and 439.20 ± 107.6 µm ($p = 0.96$), respectively.
Conclusion Adding steroid to routine anti-VEGF treatment is an effective way of treatment method for resistant DME.

Keywords Resistant macular edema · Steroid · Ranibizumab · Diabetic · Combined treatment

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Introduction

Diabetic retinopathy (DR) is the most common cause of vision loss in the 20–74 age-group in developed countries [1]. The risk of blindness is 29 times higher in diabetic patients compared to non-diabetic ones [2]. Diabetic macular edema is the most common cause of visual loss in patients diagnosed with diabetic

retinopathy [1]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy which was one of the largest and the most comprehensive one showed that 20.1% of type 1 diabetics and 25.4% of type 2 insulin-dependent diabetic patients had the visual loss within 10 years [3–5]. In addition, the Early Treatment Diabetic Retinopathy Study (ETDRS) showed that diabetic macular edema caused 24 and 6.4% moderate and severe visual loss, respectively [6]. Although the pathogenesis of diabetic macular edema (DME) is not clear, it is thought to be a result of some changes such as leakages related to retinal vessel abnormalities, localized ischemia, chronic inflammation, and vascular cell degeneration and necrosis [7]. Studies have shown that released cytokines such as vascular endothelial growth factor (anti-VEGF), TNF-alpha, intercellular adhesion molecule-1, IL-1, IL-6, and fibroblast growth factor-2 might play a role in this process [8, 9]. Therefore, corticosteroids and anti-VEGF treatments, which were active on cytokines, were used in the treatment. The corticosteroids, anti-VEGF, anti-TNF-alpha medications have been shown to inhibit the release of mediators that led to leukocyte migration and inflammation. That also showed to reduce the release of molecules such as intercellular adhesion molecule-1 [10], which is responsible for vascular endothelial cell activity and therefore be effective in the DME [11, 12]. Clinical trials have tested anti-VEGF treatments and demonstrated that the inhibitors of vascular endothelial growth factor (VEGF) have been shown to have significant efficacy in the DME treatment. Therefore, anti-VEGF has become the gold standard for the treatment of DME [13–15]. However, the majority of the eyes responded well to anti-VEGF therapy with signs of disappearing edema and visual enhancement, no optimal edema control can be ensured in some eyes, and this group was called as refractory or persistent macular edema. Some studies have shown that the prevalence is over 50% [16]. The refractor-persistent DME causes permanent disturbance for the retinal architecture that can led to permanent loss of vision due to chronic tissue stress and photoreceptor cell loss [17]. Therefore, its treatment is extremely important and various combination therapies have been tried for this purpose. In this study, the combination of anti-VEGF and sub-tenon steroid treatment was tried for this purpose. The present study aims to show whether combined anti-VEGF therapy with sub-tenon steroid therapy is superior to solely anti-VEGF therapy in the treatment of resistant DME.

Materials and methods

In this retrospective case–control series, we reviewed the medical records of patients who had been diagnosed with resistant DME between January 2014 and June 2017. We included patients who received at least three anti-VEGF injections (0.5 mg ranibizumab) within 6 months for DME at Istanbul Beyoglu Eye Education and Research Hospital. The patients were evaluated retrospectively. Patients who exhibited insufficient anatomic (over 350 μm with spectral optical coherence) and visual responses (visual gain < 3 lines) to at least six anti-VEGF treatments were randomly divided into two groups. In group I, the anti-VEGF injection was performed 10 days after the sub-tenon steroid injection [Triamcinolone acetonide (Sinakort-A®)]. And anti-VEGF was performed when needed during the follow-up period. In group II, treatment was continued with anti-VEGF only. The local ethical committee approved the study, which was conducted in accordance with the Declaration of Helsinki. All patients were informed about the potential side effects, and their consents were taken before the procedure.

Patients with additional systemic disease aside from diabetes and those who had previous eye surgery, trauma history, ischemia shown in the fluorescein angiography, glaucoma and retinal disease (epiretinal membrane, vitreoretinal traction, retinal dystrophy, etc.) were not included in the study. The DME diagnosis, defined as a clinically significant macular edema, was made based on the criteria developed by the ETDRS [6]. All patients underwent a detailed ophthalmologic examination before the treatment. The ophthalmological exam includes best corrected visual acuity (BCVA), slit-lamp examination and intraocular pressure measurement with Goldmann applanation tonometry, detailed fundus examination, and macular imaging with optical coherence tomography using the Heidelberg Spectralis® system (Heidelberg Engineering, Heidelberg Germany) by an expert retinal specialist (E.E). All the examinations and measurements were repeated after the treatment. All patients were followed up for 6 months.

Results

Seventy-two eyes of 72 patients were evaluated retrospectively. Group I and group II had 38 and 34 patients, respectively. The mean age of the patients was 58.94 ± 7.79 and 63.94 ± 8.47 in the group I and group II, respectively ($p = 0.011$). The average numbers of injections were 5.60 ± 1.26 in group I and 5.08 ± 0.28 in group II prior to the study. The mean injection numbers were 3.15 ± 0.88 and 4.61 ± 0.88 in the group I and group II, respectively ($p < 0.001$). The mean intraocular pressures were 17.71 ± 2.68 and 17.11 ± 1.22 in the group I and in the group II, respectively ($p = 0.241$).

The baseline BCVA in group I and group II was 0.51 ± 0.667 logMAR and 0.47 ± 0.60 logMAR, respectively ($p = 0.52$). In group I, at the end of 1- and 6-month follow-up BCVA improved to 0.33 ± 0.67 logMAR ($p < 0.001$) and 0.38 ± 0.60 logMAR ($p < 0.001$), respectively. In group II, at the end of 1- and 6-month follow-up BCVA improved to 0.346 ± 0.29 logMAR ($p = 0.21$) and 0.43 ± 0.60 logMAR ($p = 0.20$), respectively (Fig. 1). The baseline central macular thickness (CMT) in group I and group II was 494 ± 118.32 and 438.20 ± 90.99 µm, respectively ($p = 0.029$). In group I, at the end of 1- and 6-month follow-up, CMT decreased to 292.68 ± 48.31 µm ($p < 0.001$) and 302.57 ± 69.89 µm ($p < 0.001$), respectively. In group II, at the end of 1- and 6-month follow-up, CMT decreased to 422.26 ± 74.5 µm ($p = 0.05$) and 439.20 ± 107.6 µm ($p = 0.96$), respectively (Fig. 2). The mean BCVA change in group I and group II was 0.98 ± 0.92 logMAR and 1.55 ± 0.92 logMAR, respectively ($p = 0.013$). The mean CMT change in group I and group II was 191.52 ± 122.70 and 0 ± 113.68 µm, respectively ($p < 0.001$).

Discussion

Diabetic macular edema (DME) is the main cause of gradual vision loss in diabetic retinopathy patients. Various agents are used in the treatment of DME, including nonsteroid (anti-VEGF) and steroid (triamcinolone, dexamethasone implant, etc.) injections [18–21]. While the VEGF release is considered to be the main culprit in DME etiology, it is thought that various pro-inflammatory cytokines may be responsible for DME cases that do not respond to the serial anti-VEGF treatments and this led us to a focus on steroid therapy. The corticosteroid injections reduced macular edema via inhibiting the release of leukocytes, VEGF, prostaglandins, and other pro-inflammatory cytokines and providing capillary wall stabilization [22].

In the present study, we found that combination treatment improved BCVA from baseline

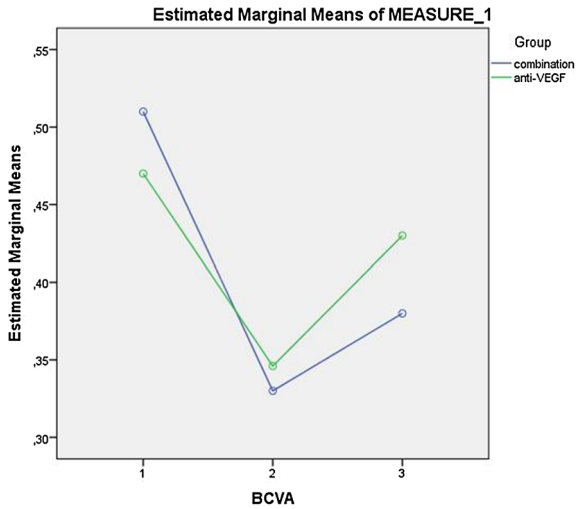

Fig. 1 LogMAR vision in pretreatment and posttreatment period (1 and 6 months after the initiation of the study). (*) statistically significant

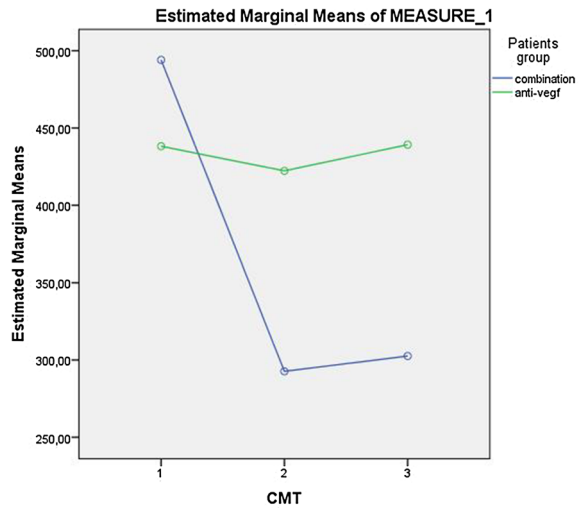

Fig. 2 CMT (µm) in pretreatment and posttreatment period (1 and 6 months after the initiation of the study). (*) statistically significant

0.51 ± 0.667 logMAR to 0.38 ± 0.60 logMAR ($p < 0.001$) and decreased CMT from baseline 494 ± 118.32 to 302.57 ± 69.89 µm ($p < 0.001$). When we compare combination treatment with solely anti-VEGF treatment, recovery of BCVA and CMT was statistically significant ($p = 0.013$ and $p < 0.001$, respectively).

Increasing IOP and cataract formation are the most common complications that were seen in the group of patients that steroids were used in terms of treatment DME [12, 23]. In the present study, there was no significant difference between the two groups in terms of IOP increase. However, dexamethasone implant is frequently used as a steroid agent in our daily routine. In a randomized study, 0.7 mg dexamethasone implant and anti-VEGF agent (bevacizumab) were compared in patients with diabetic macular edema. An increase of 10 letters or more was observed in 40% of the patients in the bevacizumab group and in 40% of the patients in the dexamethasone group. In addition, there was no reduction in visual acuity in any of the patients in the bevacizumab group, whereas in the dexamethasone group there was a reduction in vision due to cataract formation in 11% of the patients [24]. In that study, the incidence of cataracts in dexamethasone implant group was 70.3%. In the present study, a single sub-tenon steroid was administered in group I and no cataract formation was observed in any of our patient cohort. The improvement in BCVA was significantly noticed in group I, whereas there was no statistically significant increase noted in group II ($p < 0.001$, $p = 0.20$, respectively).

In the BEVORDEX study, the mean number of injections over the 12-month period was 8.6 in the bevacizumab group and 2.7 in the dexamethasone implant group [24]. In the present study, this number was 4.6 in the solely anti-VEGF group and 3.1 in the combination group, and this difference was found to be statistically significant ($p < 0.001$).

In RISE and RIDE studies, the presence of decreased BCVA in 40% of patients has shown that repeated injections were needed for an adequate therapy [25]. In the present study, however, significant changes were observed in BCVA and CMT in the sub-tenon steroid administered combination group, while there was no significant change in BCVA and CMT with anti-VEGF injection solely.

In the study by Elman et al., the patients were divided into the following four groups: group I sham injection + prompt laser, group II intravitreal ranibizumab (IVR) + prompt laser, group III intravitreal ranibizumab (IVR) + deferred laser, and group IV 4 mg IVTA + prompt laser. In a 1-year follow-up, the increase in BCVA was found significantly higher in the IVR + prompt laser group and IVR + deferred laser group compared to the IVTA and laser-only groups [26]. In addition, 55% of patients in the IVTA group needed cataract surgery, while this was needed in 12% of the patients in the IVR group. In the present study, a significant increase in BCVA was seen in the combination group compared to the solely anti-VEGF injection group. There was no intraocular pressure rise or development of cataract that required treatment in the two groups during the 6 months follow up period. In addition, changes in intraocular pressure in this study were close to each other among the groups ($p = 0.241$). However, in the study by Elman et al., a significant IOP increase was seen in 38% of the patients in the IVTA group, while this was seen only in 5% of the patients in the IVR group [26].

In recent years, intravitreal steroid (dexamethasone) implants are frequently used in diabetic macular edema which was resistant to anti-VEGF treatment. In a study by Dutra Medeiros et al. [27], it was found that maximum efficacy was seen in the third month during the 6-month follow-up period, and there was a decrease in CMT in 37% with a single injection and a mean improvement of 0.44 ± 0.27 logMAR in BCVA. That study assessed only the effect of steroids, but not the combined effect as in this study. Furthermore, in the present study it was determined that, besides its functional advantages, the anti-VEGF treatment combined with sub-tenon steroid injection reduced the number of recurrent injections when compared with anti-VEGF treatment alone. This allows patients to be treated more effectively and cheaper.

Again in another study, patients with resistant diabetic macular edema were divided into two groups, one group was treated only with intravitreal ranibizumab and the other group was treated with intravitreal ranibizumab plus dexamethasone implant. After the 6-month follow-up, an increase of 2.7 ± 9.8 letters was seen with ETDRS in the combination group and 3.0 ± 7.1 letters in the ranibizumab group, but no significant difference was found between the two groups ($p = 0.73$). The decrease in CMT was significantly noted in the combination group when

compared with the ranibizumab group ($p < 0.001$) [28]. In the present study, BCVA significantly increased in the group of ranibizumab with sub-tenon compared to the group treated with ranibizumab only ($p = 0.013$). The change in CMT was found to be decreased significantly in the combination group compared to the ranibizumab group ($p < 0.001$). This was considered to be due to the fact that there was no complication that reduced sight due to cataract after a single sub-tenon steroid injection.

The main limitation of this study is related to its retrospective design. Also, as this was a case–control study, we could not randomize the patients for two drugs. However, there are some strengths in our study, such as the large sample size and the fact that it is a single-center study. Accordingly, all patients underwent the same procedures by the same physicians.

To conclude, in our study, we can say that steroid and anti-VEGF combination treatment is beneficial in resistant diabetic macular edema. Further, long-term studies should be done to see the long-term effects of this treatment modality.

Compliance with ethical standards

Conflict of interest All authors have no financial interests to disclose. This study was not funded by any organization.

Ethical standards This retrospective study was performed in Istanbul and conducted according to the principles of the Declaration of Helsinki.

References

1. Williams GA (2012) Diabetic macular edema. In: Bandello F, Querques G (eds) ESASO course series, vol. 1. Medical retina. Karger, Basel, pp 99–104
2. International Diabetes Federation (2013) The IDF diabetes atlas, 6th edn. International Diabetes Federation, Brussels
3. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL (1984) The Wisconsin Epidemiologic Study of Diabetic Retinopathy II: prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 102:520–526
4. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL (1984) The Wisconsin Epidemiologic Study of Diabetic Retinopathy III: prevalence and risk of diabetic retinopathy when age at diagnosis is 30 and more years. Arch Ophthalmol 102:527–532
5. Klein R, Klein BEK, Moss SE, Cruickshanks KJ (1995) The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV: the long-term incidence of macular edema. Ophthalmology 102:7–16
6. Photocoagulation for diabetic macular edema (1985) Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study Research group. Arch Ophthalmol 103:1796–1806
7. Adamis AP (2002) Is diabetic retinopathy an inflammatory disease? Br J Opthalmol 86:363–365
8. Grant MB, Afzal A, Spoerri P et al (2004) The role of growth factors in the pathogenesis of diabetic retinopathy. Expert Opin Investig Drugs 13:1275–1293
9. Nguyen QDİ, Shah SM, Van Anden E et al (2004) Supplemental oxygen improves diabetic macular edema: a pilot study. İnvestig Ophthalmol Vis Sci 45:617–624
10. McGhee CN (1992) Pharmacokinetics of ophthalmic corticosteroids. Br J Ophthalmol 76:681–684
11. Massin P, Audren F, Haouchine B et al (2004) İntravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. Ophthalmology 111:218–224
12. Gillies MC, Sutter FK, Simpson JM et al (2006) İntravitreal triamsinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology 113:1533–1538
13. Brown DM, Nguyen QD, Marcus DM et al (2013) Long-terms outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RİSE and RİDE. Ophthalmology 120:2013–2022
14. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR et al (2015) Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 372:1193–1203
15. Do DV, Nguyen QD, Boyer D et al (2012) One-year outcomes of the da VINCI study of VEGF trap-eye in eyes with diabetic macular edema. Ophthalmology 119:1658–1665
16. Elman MJ, Bressler NM, Qin H et al (2011) Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 118:609–614
17. Uji A, Murakami T, Nishijima K et al (2012) Association between hyperreflective foci in the outer retina, status of photoreceptör layer, and visual acuity in diabetic macular edema. Am J Ophthalmol 153:710–717
18. Dutra Medeiros M, Postorino M, Navarro R, Garcia-Arumí J, Mateo C, Corcóstegui B (2014) Dexamethasone intravitreal implant for treatment of patients with persistent diabetic macular edema. Ophthalmologica 231(3):141–146
19. Pacella F, Ferraresi AF, Turchetti P, Lenzi T, Giustolisi R, Bottone A, Fameli V, Romano MR, Pacella E (2016) Intravitreal injection of Ozurdex(®) implant in patients with persistent diabetic macular edema, with six-month follow-up. Ophthalmol Eye Dis 8:11–16
20. Blinder KJ, Dugel PU, Chen S, Jumper JM, Walt JG, Hollander DA, Scott LC (2017) Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). Clin Ophthalmol 11:393–401
21. Shin YU, Hong EH, Lim HW, Kang MH, Seong M, Cho H (2017) Quantitative evaluation of hard exudates in diabetic macular edema after short-term intravitreal triamcinolone, dexamethasone implant or bevacizumab injections. BMC Ophthalmol 17(1):182

22. Tamura H, Miyamoto K, Kiryu J et al (2005) Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina. Invest Ophthalmol Vis Sci 46(4):1440–1444
23. Jonas JB, Degenring R, Kreissig I, Akkoyun I (2004) Safety of intravitreal high-dose reinjections of triamcinolone acetonide. Am J Ophthalmol 138:1054–1055
24. Gillies MC, Lim LL, Campain A et al (2014) A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. Ophthalmology 121:2473–2481
25. Brown DM, Nguyen QD, Marcus DM et al (2013) Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials. RISE and RİDE. Ophthalmology 120:2013–2022
26. Diabetic retinopathy clinical research network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, Ferris FL 3rd, Friedman SM, Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK (2010) Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcınolone plus prompt laser for diabetic macular edema. Ophthalmology 117:1064–1077
27. Dutra Medeiros M, Postorino M, Navarro R et al (2014) Dexamethasone intravitreal implant for treatment of patients with persistent diabetic macular edema. Ophthalmologica 231:141–146
28. Maturi RK, Glassman AR, Liu D, Beck RW, Bhavsar AR, Bressler NM, Jampol LM, Melia M, Punjabi OS, Salehi-Had H, Sun JK (2018) Diabetic Retinopathy Clinical Research Network. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: a DRCR network phase 2 randomized clinical trial. JAMA Ophthalmol 136(1):29–38