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Anti – VEGF in Treatment of Diabetic Macular Edema

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A B S T R A C T

Diabetic macular edema is the leading cause of moderate visual deterioration in patients with diabetic retinopathy. Ranibizumab) blocks vascular endothelial growth factor (VEGF) induced hyperpermeability of blood vessels. In this prospective case series we investigated the efficacy and safety of anti-VEGF treatment in reduction of central retinal thickness (CRT) and improvement in visual acuity (VA) in patients with diabetic macular edema (DME). 9 patients were followed up for 6 months and treated monthly with intravitreal ranibizumab. VA and CRT were measured at each visit. Treatment was discontinued as the peak improvement of either parameter was reached and reinstituted in case of deterioration/recurrence of edema. Study endpoints included: VA using ETDRS chart, CRT and number of injections at 6 months. Mean VA from all 9 patients increased by 0.3 lines of logMAR ($p<0.05$ compared to baseline), and CRT decreased from 515 ± 123 μm to 310 ± 110 μm. The improvement of VA after ranibizumab injection was in correlation with a decrease in CRT. Mean of 4 injections were needed to control the disease during the follow-up period. Ranibizumab treatment was effective in VA and reducing CRT. Several injections were needed to control the disease. Regular OCT examinations and retreatment are advised in order to maintain initially reached VA.

Abbreviations: DME – diabetic macular edema, VEGF – vascular endothelial growth factor, CRT – central retinal thickness, VA – visual acuity, ETDRS – early treatment diabetic retinopathy study, OCT – optical coherence tomography, SOCT – spectral domain optical coherence tomography, IDDM – insulin dependent diabetes mellitus, NIDDM – non-insulin dependent diabetes mellitus.

***Key words**: diabetic retinopathy, diabetic macular edema, anti-vascular endothelial growth factor therapy, ranibizumab*

Introduction

Diabetic retinopathy and diabetic macular edema are leading causes of visual loss and blindness of developed countries. The main reason for macular edema is leakage from blood vessels within macula. Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) showed that DME incidence in patients with insulin dependent diabetes mellitus (IDDM) with DM type II is 42%, for patients with non-insulin dependent diabetes mellitus (NIIDM) with DM type II is 24% and for patients with DM type I is 34%. Early detection of diabetic retinopathy is critical and important in DME prevention. Regulated blood glucose is the key in keeping visual acuity stabil. Retinal vascular changes have the basic role in the patophisiology of macular edema and diabetic retinopathy. Loss of pericytes and thickening of basement membrane result in incompetent retinal vasculature and increased permeability wich results in leakage in macula. Retinal vascular changes are result of chronic inflammatory process where the main role have advanced glycosilaton, oxidative stress and accumulation of intracellular sorbitol. Ranibizumab (Lucentis, Novartis) blocks vascular endothelial growth factor (VEGF) induced hyperpermeability of blood vessels. In this prospective case series we investigated the efficacy of anti-VEGF treatment in reduction of central retinal thickness (CRT) and improvement in visual acuity (VA).

Materials and methods

Nine patients were followed up for 6 months and treated monthly with intravitreal ranibizumab. On each

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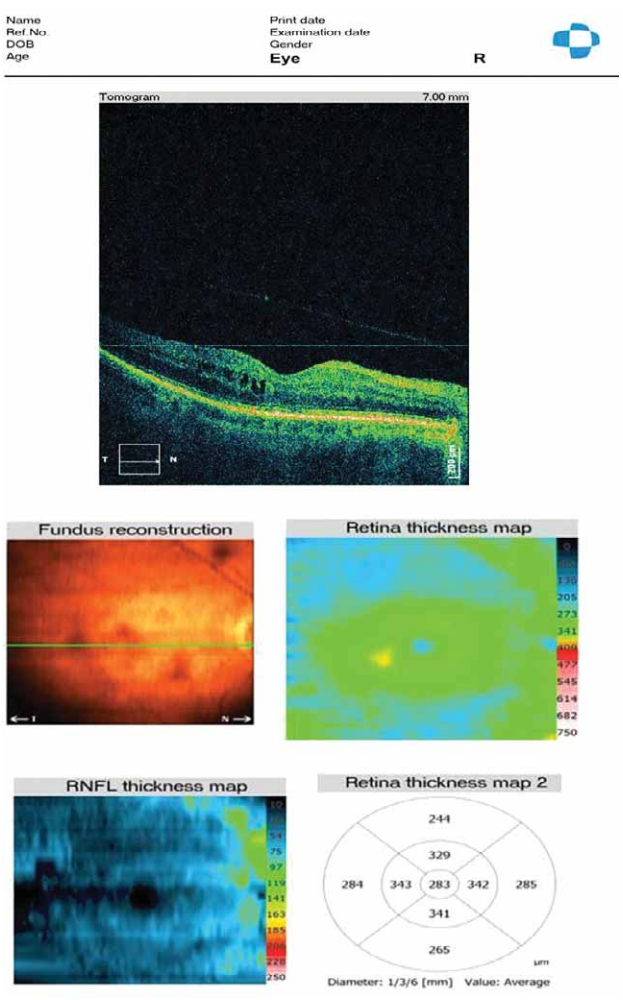

Fig. 1. Spectral domain optical coherence tomography (OCT) showing macular edema before ranibizumab.

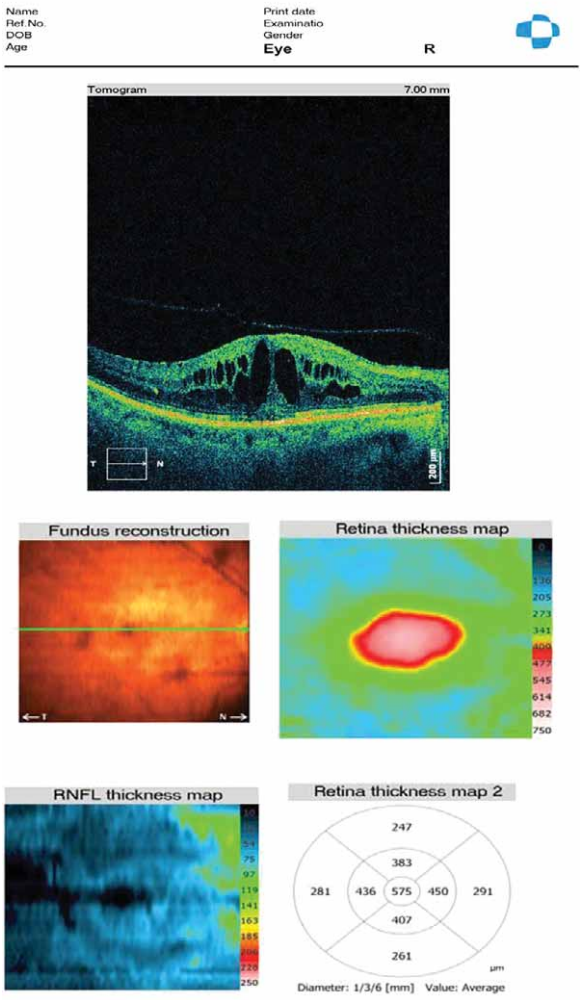

Fig. 2. Spectral domain optical coherence tomography (OCT) three weeks after ranibizumab.

examination we performed slit lamp biomicroscopy to check any anterior segment abnormalities (iris neovascularization) and fundus examination was performed using non contact lens biomicroscopy. Visual acuity (VA) was tested using early treatment diabetic retinopathy study (ETDRS) chart and central retinal thickness (CRT) was measured using Optopol SOCT 3D spectral domain optical coherence tomography (OCT). VA and OCT were measured at each visit. At the initial examination fluorescein angiography was performed to each patient. Treatment was discontinued as the peak improvement of either parameter was reached and reinstituted in case of deterioration/recurrence of edema. Study endpoints included: mean VA (logMAR), mean CRT and mean number of injections at 6 months. All intravitreal injections were performed under sterile conditions in the operating room. Ranibizumab was injected via the pars plana using 30 gauge needle.The results were compared to baseline values and statistically analyzed to see whether there is a significant change in VA and CRT when compared to baseline values.

Statistical analysis

The data were analyzed by using nonparametric student t–test to determine significance between means. The data was considered statistically significant for $p < 0.05$.

Results

At 6 months of follow-up the mean baseline VA increased by 0.3 lines from (0.6 logMAR to 0.3 logMAR). At the same time mean CRT decreased from 515±123 μm to 310±110 μm.

Mean of 4 injections were needed to control the disease during the follow-up period. After 6 months of follow-up no severe ocular (endophtalmitis, retinal detachment, uveitis) or systemic adverse events were noticed. None of the patient developed disc, iris or retinal neovascularization.

Discussion

Diabetic macular edema is the leading cause of moderate visual deterioration in patients with diabetic retinopathy. Thickening of basement membrane and reduction in the number of pericytes are believed to lead to increased permeability and incompetence of the retinal vasculature. This compromise of the blood- retinal barrier leads to the leakage of plasma constituents into the surrounding retina, with subsequent retinal edema[1]. Hypoxia is also produced by this mechanism, and it can stimulate the production of vascular endothelial growth factor (VEGF), which is up-regulated in diabetic macular edema and proliferative diabetic retinopathy. Ranibizumab is a recombinant humanized antibody fragment that is active against all isoforms of VEGF-A. Intravitreal ranibizumab is FDA approved for the treatment of exudative ARMD. In the RESOLVE study 151 patients were randomized 1:1:1 to ranibizumab monotherapy at a dose of 0.3 mg or 0.5 mg or sham treatment. Patients received an initial treatment of 3 consecutive monthly injections and were followed monthly with an as-necessary regimen from month 3 to month 12. At month 12, a mean increase in best corrected visual acuity (BCVA) of 11.8 letters in the 0.3-mg group and of 8.8 letters in the 0.5-mg group was noted, as compared with a reduction in BCVA of –1.4 letters in the sham group[2]. In the READ-2 study 126 patients were randomized 1:1:1 to receive 0.5 mg of ranibizumab, focal/grid laser coagulation, or a combination of ranibizumab and laser. At month 6, the mean gain in BCVA was significantly greater in the ranibizumab monotherapy group, with +7.2 letters, compared with the laser monotherapy group, who lost –0.4 letters and the combination treatment group, gaining only +3.8 letters[3].

In the RESTORE study (phase 3, laser-controlled, randomized, multicenter study), 345 patients were randomized 1:1:1 to 0.5 mg ranibizumab plus sham laser, 0.5 mg ranibizumab plus active laser, or sham injections with active laser. A treatment initiation phase included 3 consecutive monthly intravitreal injections of either ranibizumab or sham. Subsequently, an as-necessary regimen was followed from month 3 to month 12. The mean change in BCVA from baseline to months 1–12 was +6.1 letters in the ranibizumab monotherapy group, +5.9 letters in the group receiving combination therapy with ranibizumab and laser, and +0.8 letters in the laser alone group[4].

Conclusion

Results from our study are compatible with those from RESOLVE, READ-2 and RESTORE trials. Ranibizumab appears to be both safe and well tolerable in improving visual acuity in patients with macular edema secondary to diabetic retinopathy. Further clinical trials with larger number of patients, longer follow-up and treatment duration are needed to confirm efficacy and also safety of ranibizumab in treatment od diabetic macular edema.

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ANTI – VEGF TERAPIJA U LIJEČENJU DIJABETIČKOG MAKULARNOG EDEMA

SAŽETAK

Edem makule jest glavni uzročnik smanjene vidne oštrine kod pacijenata oboljelih od dijabetičke retinopatije. Ranibizumab (Lucentis, Novartis) blokira vaskularnim endotelnim faktorom rasta (VEGF) induciranu hiperpermeabilnost krvnih žila U ovoj studiji istražili smo efikasnost anti –VEGF terapije u redukciji centralne retinalne debljine (CRT) i poboljšavanju vidne oštrine. 9 pacijenata je praćeno 6 mjeseci i liječeno mjesečnim dozama intravitrealnog ranibizumaba.VA and CRT su mjereni prilikom svake kontrole. Liječenje je prekinuto kada je jedan od promatranih kriterija

(VA i CRT) maksimalno poboljšan i ponovo nastavljena prilikom ponovne pojave edema u makuli. Promatrani ciljevi studije uključivali su: vidnu oštrinu (VA) mjerenu ETDRS tablicama, centralnu retinalnu debljinu (CRT) i broj injekcija unutar 6 mjeseci praćenja. Rezultati su pokazali da je vidna oštrina kod svih 9 pacijenata porasla za 0.3 logMAR reda ($p<0.05$ prema početku). Poboljšanje vidne oštrine nakon injekcije ranibizumaba bilo je u korealciji sa smanjenjem CRT. Tijekom vremena praćenja od 6 mjeseci bilo je potrebno prosječno 4 injekcije da bi se postigla kontrola bolesti. Injekcije ranibizumaba pokazale su se efikasne u poboljšavanju vidne oštrine i smanjenju centralne retinalne debljine.