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Intravitreal ranibizumab for non-responding laser photocoagulation in diabetic macular edema-case series

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Abstract: We report our experienced treating diabetic macular edema (DME) patients with intravitreal ranibizumab that not responding to laser photocoagulation. A retrospective case series of DME patients that not responding to focal / grid laser photocoagulation, treated with intravitreal ranibizumabat Hospital University Sains Malaysia from 2011 to 2012. Best corrected visual acuity (BCVA), intraocular pressure (IOP) and central macular thickness (CMT) measurement were performed pre and post intravitreal ranibizumab. Six patients (7 eyes) were included in this case series. All eyes received one injection of intravitreal ranibizumab (0.3mg). Mean logarithm of the minimum angle of resolution (Log MAR) BCVA was 1.2 pre intravitreal ranibizumab and improved to 0.88 at 6 months post injection. Mean CMT was 520 µm pre intravitreal ranibizumab and reduced to 425 µm at 6 months post injection. None of the eye showed any significant raised in IOP post injection. In this small numbers of DME cases, we observed that intravitreal ranibizumab results in improvement of the visual acuity and reduction in CMT in DME patients that not responding to focal / grid laser photocoagulation.
Keywords: Diabetic macular edema, laser photocoagulation, intravitreal, ranibizumab.

INTRODUCTION

Diabetic macular edema (DME) is the most common cause of central visual loss in diabetic retinopathy. DME is caused by increase vascular permeability resulting in the leakage of plasma constituents and deposition of hard exudates at the macula. It results in central retinal thickening and visual distortion. DME can be further classified into focal and diffuse. Focal macular edema is characterized by focal leakage from micro aneurysm with circinate intraretinal hard exudates. Diffuse macular edema is characterized by generalized macular edema resulted from dilated retinal capillaries with cystoids spaces formation.

Traditionally, laser photocoagulation remained the gold standard in the treatment of DME. The Early Treatment Diabetic Retinopathy Study (ETDRS) group demonstrated that eyes with macular edema benefited from immediate laser photocoagulation, which significantly reduces the risk of moderate visual loss. Focal macular edema is more amenable from focal laser whereas diffuse macular edema responded to grid laser [1]. However, previous studies have shown that eyes with diffuse macular edema carry a poor prognosis despite laser photocoagulation [2, 3]. Furthermore, additional laser treatment may have risk of permanent visual damage in persistent leaking micro aneurysm located very close to foveal avascular zone [1].

Vascular endothelial growth factor (VEGF) was found to increase the vascular permeability over the vascular endothelial cells junction resulting in DME [4]. Ranibizumab has been recently available for treatment of visual impairment due to DME [5]. Ranibizumab is a humanized monoclonal antibody fragment that binds all active forms of VEGF offers an entirely new pharmacological approach for treatment of visual impairment due to DME compared to argon laser therapy [6].

We report our experienced treating DME patients with intravitreal ranibizumab that not responding to laser photocoagulation.

CASE STUDY

This was a retrospective case series of patient with DME that not responding to focal / grid laser photocoagulation was treated with one injection of intravitreal ranibizumab (0.3mg) at Hospital University Sains Malaysia from 2011 to 2012.

All patients had type 2 diabetes mellitus with clinical significant macular enema (CSME) as defined by ETDRS [1]. Patients who had the following criteria

were excluded from the study (i) macular ischemia >1000um, (ii) presence of any other macular pathology such as age related macular degeneration, retinal vascular occlusive disease, (iii) presence of vitreomacular traction, (iv) presence of epiretinal membrane, (v) advance glaucoma or other optic disc pathology.

Best corrected visual acuity (BCVA), intraocular pressure (IOP) and central macular thickness (CMT) were performed pre intravitreal ranibizumab, and at 1,3 and 6 months post injection. BCVA were converted to the logarithm of minimal angle of resolution (log MAR). Heidelberg Spectralis® optical coherence tomography (OCT) was used to assess the macular thickness by using the 6 mm Fast Macular mapping. CMT is the mean retinal thickness of circular 1-mm diameter central retina, was taken for analysis in this study.

There were 6 patients (7 eyes) with DME that not responding to focal / grid laser photocoagulation who fulfilled the criteria were enrolled into this case series. The mean age was 60.8 years. There were 3 male and 3 female. Only 3 patients were completed follow-up till 6 months, and the other 3 patients defaulted follow-up at month-3 (1 patient = 1 eye) and month-6 (2 patients = 3 eyes).

All eyes received one injection of intravitreal ranibizumab (0.3mg). Mean log MAR BCVA was 1.2 pre intravitreal ranibizumab and improved to 0.88 at 6 months post injection. Mean CMT was 520 µm pre intravitreal ranibizumab and reduced to 425 µm at 6 months post injection. None of the eye showed any significant raised in IOP post injection (Table-1).

Table 1: Mean BCVA, IOP and CMT at pre and post intravitreal ranibizumab.

	Pre intravitreal ranibizumab	Post intravitreal ranibizumab		
	(n = 7 eyes)	1 Month (n = 7 eyes)	3 Months (n = 6 eyes)	6 Months (n = 3 eyes)
Mean log MAR BCVA	1.2	0.84	0.96	0.88
Mean IOP (mmHg)	15	16	17	15
Mean CMT (µm)	520	409	456	425

Abbreviation: Logarithm of the minimum angle of resolution (log MAR), best corrected visual acuity (BCVA), intraocular pressure (IOP), central macular thickness (CMT)

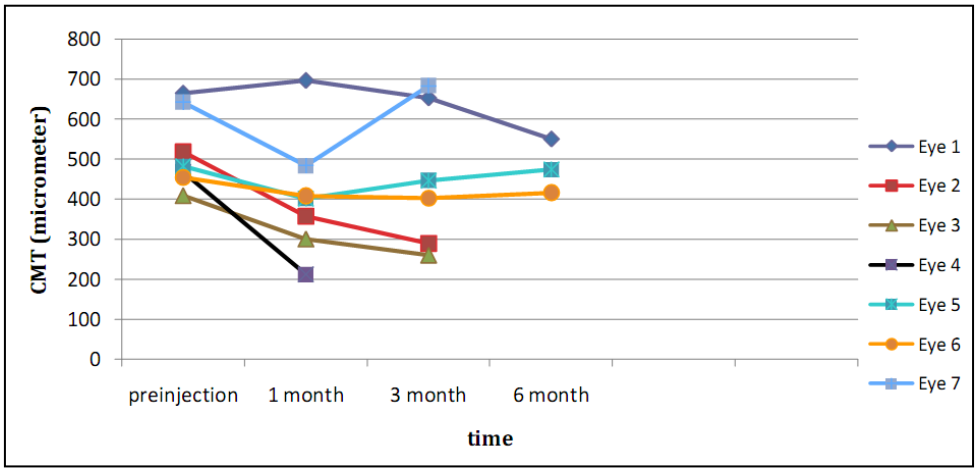

Fig-1: Central macular thickness (CMT) at pre and post intravitreal ranibizumab for each eye.

Figure 1 showed the mean CMT for each eye pre intravitreal ranibizumab, and at 1, 3 and 6 months post injection. There was no incidence of endopthalmitis and no other complications related to intravitreal ranibizumab were observed.

DISCUSSION

There was improvement of BCVA at 6 month post intravitreal ranibizumab. In this small case series of DME patients that poor respond to laser therapy showed reduction of macular thickness after one month of intravitreal anti VEGF. Three eyes showed encouraging anatomical outcome as CMT decreased by 115 to 148 µm at the 6 months of follow up.

Our finding was similar to other studies [7, 8]. Chun et al shown that intravitreal ranibizumab reduced the retinal thickness and improved the BCVA at 2 years follow up [7]. It was supported by Nguyen et

al which show similar finding at 9 months follow up [8].

Ranibizumab was generally well tolerated in DME clinical studies, either when given as monotherapy or when combined with laser treatment [7]. The approval of ranibizumab was based on data from two famous clinical trials, RESTORE and RESOLVE study, which showed that ranibizumab was superior in providing rapid and sustained visual acuity gain versus sham therapy or laser therapy, the current standard of care [5, 9]. A report by DRCR.net in year 2010 also found that intravitreal ranibizumab with either prompt or deferred laser had better visual acuity outcomes compared with prompt laser alone [10]. The vision improvement for many of these patients was clinically significant, meaning that they regained the ability to carry out day-to-day activities such as driving.

There was no complication related to intravitreal ranibizumab and none of our cases showed any incidence of endopthalmitis post intra vitreal ranibizumab. The incidence of endophthalmitis associated with intravitreal ranibizumab was 0.02% [11].

Despite proven benefit of ranibizumab, its relative high cost treatment restricts some patient from treatment of DME. Another anti VEGF agent which is comparatively lower cost, intravitreal bevacizumab provide stability or improvement in BCVA at 24 months [12, 13].

Limitation of this study is small number of patients and short follow up period. Furthermore, this retrospective case series with no control group, cannot rule out benefit from laser photocoagulation given prior to intravitreal anti VEGF in which study had shown anatomical improvement may be observed after a 4 month follow-up [14]. Future study with larger sample size either with multi-center or longer period of study should overcome this.

CONCLUSION

In this small numbers of DME cases and limited period of follow up, we observed that a single intravitreal ranibizumab results in improvement of the visual acuity and CMT in patient that not responding to focal / grid laser photocoagulation.

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