·Letter to the Editor·

Intensified intravitreal bevacizumab treatment regime for type 1 and 2 idiopathic macular telangiectasia

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Received: 2015-06-18 Accepted: 2015-10-29

DOI:10.18240/ijo.2016.07.23

Chryssafis C, Neubauer AS, Papadopoulos E, Januschowski K, Boden KT, Szurman P. Intensified intravitreal bevacizumab treatment regime for type 1 and 2 idiopathic macular telangiectasia. *Int J Ophthalmol* 2016;9(7):1076-1078

Dear Sir,

I am Dr. Christos Chryssafis, from the Knappschafts Eye Clinic, Sulzbach, Saar, Germany. I write to present the results of our study about an intensified intravitreal bevacizumab (IVB) injections regime for type 1 and 2 idiopathic macular telangiectasia (IMT). Treatment by thermal laser photocoagulation, photodynamic therapy, intravitreal triamcinolon and retinal surgery was not very successful[1-2] and none of these treatment modalities have yet been accepted as a gold standard. Vascular endothelial growth factor (VEGF) is supposed to play an important role in the pathogenesis and natural course of IMT [3]. Optimal scheme and treatment duration of anti-VEGF therapy for IMT is unknown, especially with regard to long-term follow-up[1-2,4]. Therefore the aim of this study was to evaluate the functional and morphological treatment effects of an intensified, standardized IVB injection regimen in eyes with IMT with a long-term follow-up. Optimal number of bevacizumab injections and success predictors were investigated. This retrospective interventional case series conformed to the tenets set forth in the Declaration of Helsinki. All patients were recruited from a single vitreoretinal referral center (Knappschafts Augenklinik Sulzbach/Saar, Germany). All patients completed informed consent for ophthalmic imaging and signed informed consent for the off label use of IVB in IMT and its potential risks. In the study period (November 2010 to February 2014) a total of 28 eyes of 21 consecutive patients (15 males and 6 females) with IMT (type one or non-proliferative type two IMT) were included. Non proliferative stage of type 2 disease was included. Any other ocular retinal pathology or history of vitreoretinal surgery or pretreatment of any types were exclusion criteria. Injections of 0.05 mL (1.25 mg) bevacizumab were performed following the recommended standard protocol under sterile conditions. The patients were divided into two subgroups. The first one (subgroup A) consisted of 18 eyes (13 patients) who received maximal 4 injections and the second one (subgroup B) consisted of 10 eyes (9 patients) who received at least 5 injections. In all patients bevacizumab injections were performed on a monthly basis until either retinal edema was not visible in the OCT measurement or no further visual acuity changes were seen. Retreatment was decided on a monthly basis as a *pro reo nata* (PRN) regime, based on best corrected visual acuity (BCVA), fundus examination and OCT examination. All patients received examinations of BCVA, ophthalmoscopy and spectral domain OCT during each follow up visit. Patients were examined at baseline, 4wk after every injection and 3mo after the last injection. Fluorescein angiography (FA) was performed at baseline in order to secure or establish the diagnosis. For FA, a Topcon Angiograph (Japan) was used. The size of early stage (1min) and late stage (5min) hyperfluorescent areas of the perifoveal macular region was assessed. All OCT measurements were performed using the Spectralis HRA OCT (Heidelberg Engineering, Germany). Foveal thickness and temporal maximal macular thickness were calculated in this study at baseline, 4wk and 3mo after the last injection. Statistical analysis was performed with the software program SPSS v21.0 (IBM, Armonk, New York, USA). P <0.05 was considered statistically significant. Primary endpoint of the study was the evaluation of the visual acuity changes before and after the repeated form of IVBs and a possible correlation with the number of injections. Secondary endpoint was the evaluation of foveal thickness and maximal temporal macular thickness changes before and after the repeated IVBs and possible correlation with the number of injections. Unilateral type 1 disease was observed in 14 patients (12 males and 2 females). Bilateral type 2 IMT had 7 patients (3 males and 4 females). Mean injections number was 4.2 with a mean follow up time of

Table 1 Descriptive data of the patients

Group	No. of eyes	Age (a)	Gender (M/F)	Baseline VA (logMAR)	Min/max VA (logMAR)	OCT foveal baseline (μm)	OCT temporal baseline (μm)	No. of injections	Follow-up (mo)	VA at last follow-up (logMAR)	OCT foveval follow-up (μm)	OCT temporal follow-up (μm)
Total	28	70.71	15/6	0.33	0.70/0.10	263	356	4.21	10.95	0.36	249	353
Type 1	14	68.93	12/2	0.26	0.50/0.10	294	375	5.71	11.28	0.34	281	383
Type 2	14	74.29	3/4	0.39	0.70/0.10	239	338	2.50	10.28	0.32	218	323
Subgroup A	18	73.83	9/4	0.36	0.70/0.10	265	355	2.28	8.31	0.30	241	335
Subgroup B	10	67.60	6/3	0.26	0/70/0.00	261	360	7.70	14.11	0.45	265	385

10.95 (1-40)mo. The descriptive data of the patients are illustrated in Table 1.

Patients in subgroup B (mean 7.7/5-12 injections) (10 eyes of 9 patients) had a deterioration in mean BCVA logMAR from 0.26 (SD 0.11) to 0.45 (SD 0.28). This deterioration was statistically significant (P=0.005; t-test). Mean BCVA logMAR of the subgroup A patients (mean 2.2/1-4 injections) (18 eyes of 13 patients) improved from 0.36±0.22 to 0.30±0.17. This improvement was statistically significant (P=0.003; t-test). Mean foveal thickness of the subgroup B showed no change (261±64 μm *vs* 265±115 μm) with no statistical significance (P=0.342). The maximal temporal macular thickness showed a small increase (360±64 μm *vs* 385±93 μm) that was not statistically significant (P=0.195). Mean foveal thickness in the subgroup A showed a slightly decrease (265±104 μm *vs* 241±86 μm). This decrease was not statistically significant (P=0.34). The maximal temporal macular thickness showed a decrease (355±75 μm *vs* 335±65 μm) that was not significant (P=0.19). In the ANOVA analysis, the number of injections correlated statistically significant with the OCT foveal thickness changes (P=0.005) and the temporal maximal macular thickness changes (P=0.042). The number of injections also showed a statistically significant negative correlation with the baseline logMAR visual acuity (r=-0.268) and a significant correlation with logMAR visual acuity change in follow up (P=0.0001) (Figure 1).

Baseline logMAR visual acuity has been shown as a predictor for the number of injections needed and correlated with the final visual acuity (P=0.044) (Figure 2).

The type of IMT correlated significantly (P=0.01) with the number of injections necessary, but did not correlate with either visual acuity, visual acuity improvement nor thickness measures.

In our study it has been shown that repeated IVBs in the subgroup B for type 1 and non-proliferative type 2 IMT resuited in a functional decrease of BCVA over a follow up period of 40mo. In the subgroup A, the BCVA increased statistically significant. While OCT parameters and type of IMT were less relevant for the visual outcome, number of injections and initial BCVA before treatment were important. To our knowledge, this is the first study in the literature examining an intensified treatment regime over a time period of 40mo.

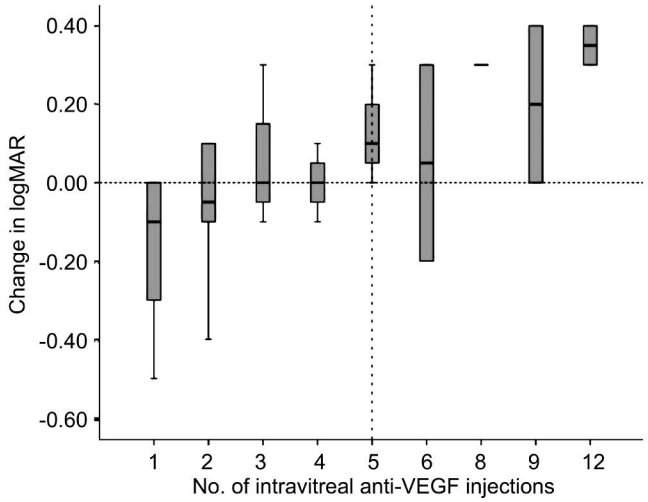

Figure 1 Number of intravitreal injections necessary and visual acuity improvement In the group of 5 or more intravitreal injections an improvement is very unlikely.

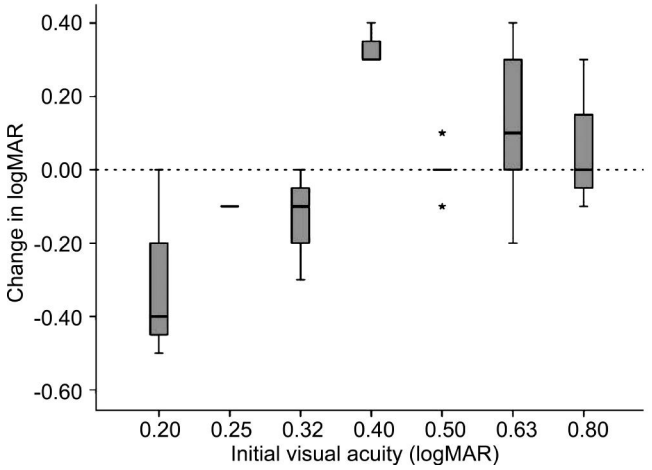

Figure 2 Initial visual acuity predicts change in visual acuity with intravitreal therapy In patients with a relatively good initial acuity of better than 0.32 logMAR visual acuity improvements with intensified anti-VEGF injections are likely.

Our results should generally be regarded critically in light of the retrospective character and the absence of patients suffering from type 2 proliferative disease. The rather high number of patients included, the long follow up period and the uniform treatment regime are strengths of this study. Our data are supported by other reports showing the benefit of singular or multiple injections in patients with type 1 IMT[5-6] and for patients with non proliferative type 2 IMT [1,7-9]. Other studies contradicting our results exist and showed no

morphological and functional significant benefit of the use of repeated anti-VEGF treatment in IMT[4,10].

It is likely that patients with IMT type 1 with pronounced macular edema from leaky telangiectasis may benefit functionally and morphologically from intravitreal anti-VEGF injections [5] reported similar results. Our study indicates that this benefit can be sustained over a quite longer period of 40mo. Takayama *et al* [10] for example proposed that IVB did not improve visual acuity or thickness in type 1 IMT and type 2 respectively. Compared to our study, the number of eyes included (5 eyes) and the shorter follow up perior (12mo) could explain the different results obtained. For type 2 non proliferative IMT Meyer-ter-Vehn *et al* [4] found further typical changes with retinal atrophy and intraretinal cysts on OCT. Sigler *et al*[1] reported also remain of inner retinal cysts and a disrupted foveal outer nuclear layer. Matt *et al* [11] reported a moderate morphological effect of IVBs but some individual patients experience a long-term benefit. This supports our finding, that OCT thickness was not relevant for visual outcome but rather initial BCVA and number of injections.

In Table 1, it is showed that patients with type 2 IMT received better visual improvement than type 1 patients after treatment. Besides, subgroup A mainly consisted of patients with type 2 MIT (11 of 18 eyes) and most patients in subgroup B are type 1 (7 of 10 eyes). The better effect and the fewer number of injections in type 2 IMT could maybe suggest that the different pathogenesis of the two types may play a role to the response and sensitivity to the bevacizumab treatment.

A forced (repeated) IVB injections regime for the treatment of type 1 and type 2 (non proliferative) IMT with a strict follow up and a PRN injection scheme should be considered as a treatment option for the patients. In our study with a forced form of maximal 4 IVB injections (one every four week) a functional improvement of the logMAR baseline visual acuity and a slightly morphological reduction of the foveal and maximal temporal macular thickness were seen. The baseline visual acuity seems to be an important predictive indicator for the number of injections needed.

ACKNOWLEDGEMENTS

Conflicts of Interest: Chryssafis C, None; **Neubauer AS,** None; **Papadopoulos E,** None; **Januschowski K,** None; **Boden KT,** None; **Szurman P,** None.

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