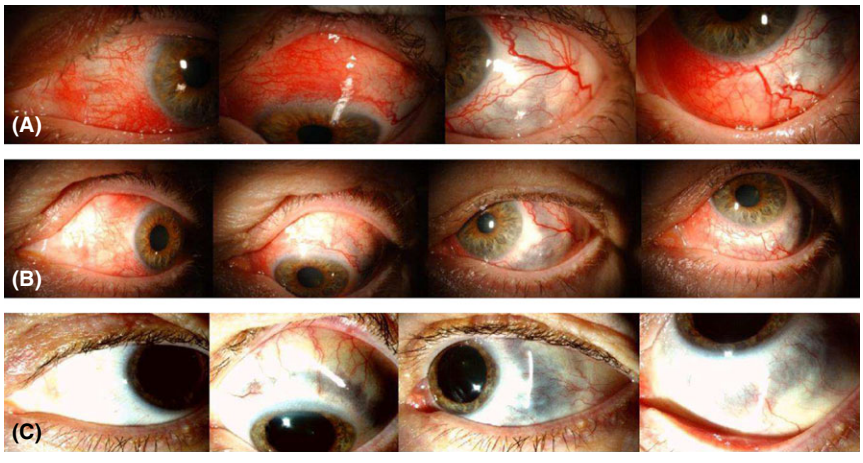

Fig. 1. Photographs of the patient at the beginning of the inpatient treatment in April 2012 (A), after the 3rd Tocilizumab application in June 2012 (B), and at last presentation in March 2014 (C).

patient with severe therapy-refractive one-sided anterior necrotizing scleritis with no known systemic rheumatological disorder. Initially, the patient complained about anterior scleral and conjunctival injection and little pain of the left eye, headache and subjectively unaltered vision of 0.7 decimal. The patient received local steroid therapy, which did not alter the disease. Two weeks later the patient presented with massive disease progression, including thinning of the sclera. Treatment was then increased to systemic steroid therapy (40 mg methylprednisolone daily, weekly reduced by 10 mg), which showed no beneficial effect. In accordance with rheumatological recommendations, therapy was escalated to anti-TNF-α (Infliximab) application. This treatment still did not change the course of disease and vision even dropped to 0.5 decimal. As scleritis worsened and necrosis increased, in April 2012 (see Fig. 1) an interdisciplinary inpatient therapy was initiated. The combination of anti-IL-6 (Tocilizumab 480 mg every month) and steroid bolus (Prednisolone 500 mg for 3 days, 250 mg for 2 days, then slowly reducing) showed to be effective. The patient was dismissed from the clinic with reduced scleritis and stopped necrosis 1 week after the anti-IL-6 treatment was started. After the sixth Tocilizumab infusion, in September 2012, the patient presented with no inflammatory signs. Steroid therapy was reduced and discontinued in February 2014. Until now, the patient has been free from any relapse of disease; the decimal visual acuity is 0.8.

Within the last 6 years, 9 of 10 patients with anterior necrotizing scleritis at our clinic received multiple anti-inflammatory and immunosuppressive drugs, four of which did not benefit from most of the currently available treatments. Anti-TNF-α agents showed no effect in 3 of 4 cases. Anti-CD20 Rituximab did not help in 2 of 2 cases. Cyclophosphamide did not stop necrosis in 2 of 4 patients (J. Tode, unpublished).

The presented single case report indicates a putative alternate therapy regime for patients with treatment-resistant anterior necrotizing scleritis. It provides evidence that anti-IL-6 therapy with Tocilizumab can be an effective drug in alleviating this rare disease. However, from this case one cannot differentiate whether Tocilizumab alone, the steroid bolus therapy or the combination of both is the driving mechanism to the cure.

Not much is known about anti-IL-6 treatment in autoimmune inflammation of the eye. There are no data about Tocilizumab treatment in scleritis and only little data about Tocilizumab treatment in uveitis (Tappeiner et al. 2012). One can only assume that autoimmune scleritis is linked to processes known from autoimmune uveitis and non-articular manifestations of arthritis and that IL-6 could play an important role in this disease.

The presented case report is to date the first case of anti-IL-6 treatment in anterior necrotizing scleritis. It shows the need for further research and shall put emphasis on the possibility of Tocilizumab treatment in rare autoimmune eye diseases. The potential of anti-IL-6 therapy is large, as side-effects are estimated to be little and the need for new therapeutic alternatives is unmatched.

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Effect of intravitreal bevacizumab on macular and peripapillary choroidal thickness in injected and fellow eyes of patients with diabetic macular oedema

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Editor,

Diabetic retinopathy (DR) is the leading cause of vision loss in working-age patients around the world. Diabetic macular oedema (DMO) is the most common cause of

visual impairment in type 2 diabetes. Currently, intravitreal injection of bevacizumab (IVB), a vascular endothelial growth factor (VEGF) antibody, is one of the most accepted treatments.

Although major changes in diabetic eyes occur in the retinal vessels, additional changes may be observed in the choroidal layer, a vascular bed that supplies blood to the outer retina. A structurally and functionally normal choroidal vasculature is essential for the retina; abnormal choroidal blood volume or compromised flow may result in photoreceptor cell damage.

Here, we assessed the effect of IVB on choroidal thickness (CT) in injected and fellow eyes of patients with DMO.

This prospective study included 44 (88 eyes) patients with diabetes mellitus (DM). Macular oedema (MO) was treated with intravitreal injection of bevacizumab (Altuzan; Genentech, San Francisco, CA, USA). The research was approved by Institutional Review Board (IRB: 2013-126). Optical coherence tomography (Retinascan Advanced RS-3000; NIDEK, Gamagori, Japan) measurements were performed before IVB, at first and at 7th day after the injection. Retinal thickness (RT) $\geq$ 300 μ involving the central zone was defined as MO. Choroidal thickness was measured as the perpendicular distance between the outer border of the retinal pigment epithelial layer (RPE) and the sclero-choroidal interface, manually drawn by the examiner.

The normal distribution of the parameters was tested using the Kolmogorov–Smirnoff test. As the data were not normally distributed, significant differences were evaluated using Wilcoxon signed-rank test. A p value of <0.05 was considered statistically significant.

Mean age of the patients was 62.0 ± 9.7 years. All patients had type 2 DM. The duration of DM was 14.8 ± 6.2 years. Eighteen (40.9%) of the injections were performed in the right eye and 26 (59.9%) in the left eye.

In injected eyes, foveal RT decreased significantly at first and at 7th day. Macular CT showed a significant decrease at first day inferior to the fovea. Peripapillary CT significantly decreased at first day at whole peripapillary, upper and lower hemifields, and temporal, nasal and inferior quadrants. In fellow eyes, macular CT significantly decreased inferior to the fovea at first week and peripapillary CT significantly decreased at temporal quadrant at first day. In both eyes, macular and peripapillary CT increased within 7 days (Table 1).

Adhi et al. (2013) have found that subfoveal CT and subfoveal choroidal vessel layer and choriocapillaris layer thickness were significantly reduced in eyes with DR. Kim et al. (2013) have shown that CT increased significantly as the severity of DR worsened. The subfoveal choroid was thicker in eyes with DME. The mechanism of choroidal thinning in early DR and choroidal thickening in advanced DR has not been identified yet. It was proposed that thinning of the choroid may be due to vascular constriction or choriocapillaris loss secondary to hypoxia and choroidal thickening may be the result of choroidal vasodilatation or increased flow mediated by VEGF (Kim et al. 2013).

Choroidal VEGF is secreted from the RPE, diffuses through Bruch's membrane and enters the choriocapillaris (Saint-Geniez et al. 2006). The choroidal effects of VEGF include increase in permeability, angiogenesis and maintenance of the choroidal vasculature (Marneros et al. 2005). In injected eyes, the decrease in CT was more prominent at the peripapillary area. Johnson et al. (2005) have described peripapillary choriocapillaris non-perfusion in choroidal circulation in diabetic monkeys. We may hypothesize that blocking VEGF may have an impact on choroidal vasculature resulting in choroidal thinning. Due to the short half-life of bevacizumab in the vitreous, the effect of IVB was transient on CT in this study.

In conclusion, the findings of the study revealed that CT decreases

Table 1. Comparison of macular and peripapillary choroidal thickness changes at 1st and 7th day following the injection (Wilcoxon signed-rank test).

		Injected eyes (n = 44)					Fellow eyes (n = 44)				
		Baseline	1st day	7th day	p values		Baseline	1st day	7th day	p values	
FRT (μ) (Mean ± SD)		417.8 ± 129.1	380.4 ± 115.1	366.4 ± 102.9	0.011	0.011	328.9 ± 99.6	325.8 ± 95.0	321.9 ± 100.9	0.599	0.503
Macular choroidal thickness (μ) (Mean ± SD)	SubF	258.9 ± 74.6	243.8 ± 66.6	249.4 ± 66.4	0.487	0.476	243.4 ± 61.4	238.6 ± 71.2	239.6 ± 59.5	0.586	0.280
	T1	240.4 ± 60.0	235.2 ± 55.5	230.1 ± 52.0	0.645	0.201	233.1 ± 66.0	228.1 ± 68.7	231.4 ± 61.9	0.305	0.979
	T2	225.0 ± 48.3	221.4 ± 58.1	216.6 ± 63.2	0.902	0.138	216.2 ± 56.6	209.0 ± 60.8	214.1 ± 56.5	0.416	0.226
	N1	241.8 ± 80.2	230.4 ± 69.0	229.8 ± 59.8	0.767	0.356	229.6 ± 57.1	229.2 ± 71.1	229.3 ± 60.6	0.651	0.861
	N2	196.4 ± 58.7	186.2 ± 56.6	193.5 ± 42.6	0.538	0.814	192.8 ± 65.3	191.8 ± 56.6	190.1 ± 50.6	0.645	0.241
	S1	232.1 ± 57.8	216.1 ± 44.2	229.2 ± 48.4	0.062	0.991	241.8 ± 56.8	239.1 ± 54.2	239.2 ± 58.4	0.200	0.229
	S2	215.2 ± 47.6	205.3 ± 47.7	208.5 ± 45.0	0.809	0.304	220.5 ± 52.5	218.3 ± 48.6	219.5 ± 46.2	0.072	0.235
	I1	246.0 ± 70.6	223.1 ± 52.1	228.4 ± 65.5	0.011	0.082	251.9 ± 74.6	248.1 ± 62.9	248.4 ± 63.4	0.073	0.013
	I2	220.1 ± 54.8	210.3 ± 52.1	214.7 ± 49.2	0.149	0.977	226.5 ± 65.9	221 ± 61.1	222.7 ± 59.1	0.107	0.089
Peripapillary choroidal thickness (μ) (Mean ± SD)	WholP	183.1 ± 44.7	169.8 ± 39.8	174.5 ± 42.4	0.004	0.286	171.5 ± 48.5	165.2 ± 40.1	166.2 ± 42.0	0.528	0.169
	UpH	188.8 ± 45.4	176.7 ± 45.2	182.9 ± 45.9	0.045	0.617	172.7 ± 45.4	170.1 ± 42.2	171.9 ± 43.8	0.904	0.662
	LowH	177.6 ± 47.4	162.9 ± 41.3	166.0 ± 43.6	0.008	0.170	166.3 ± 47.3	162.4 ± 42.3	163.0 ± 44.5	0.176	0.156
	T	187.0 ± 52.0	167.2 ± 38.9	174.2 ± 48.5	0.001	0.310	173.7 ± 45.6	169.2 ± 41.9	171.2 ± 43.2	0.039	0.246
	N	191.3 ± 49.9	175.5 ± 44.7	182.5 ± 47.0	0.008	0.172	176.7 ± 53.4	171.0 ± 44.0	173.9 ± 48.0	0.700	0.753
	S	186.6 ± 48.1	179.1 ± 54.3	183.0 ± 51.9	0.267	0.995	170.3 ± 44.3	169.7 ± 45.3	170.3 ± 44.3	0.913	0.870
	I	169.6 ± 47.4	156.2 ± 43.5	157.8 ± 42.7	0.036	0.168	159.2 ± 46.2	156.2 ± 45.5	157.1 ± 46.4	0.074	0.259

FRT = foveal retinal thickness, SubF = subfoveal, T1 = 500 μ temporal, T2 = 1000 μ temporal, N1 = 500 μ nasal, N2 = 1000 μ nasal, S1 = 500 μ superior, S2 = 1000 μ superior, I1 = 500 μ inferior, I2 = 1000 μ inferior, WholP = whole peripapillary, UpH = upper hemifield, LowH = lower hemifield, T = temporal, N = nasal, S = superior, I = inferior.

transiently, particularly in the peripapillary area, following IVB in the treated eyes of patients with DMO.

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Uveitic macular oedema after treatment with vemurafenib

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Editor,

Vemurafenib is a potent kinase inhibitor approved for the treatment of metastatic cutaneous melanoma. It inhibits the serine/threonine protein kinase B-raf encoded by a gene that carries a specific mutation, the so-called V600 mutation. Survival in patients with BRAF V600-mutant metastatic cutaneous melanoma is dramatically better with this drug than with classic chemotherapy (Sosman et al. 2012). However, mild uveitis was described as an adverse effect in 4% of cases in pivotal clinical trials of vemurafenib (Choe et al. 2014). We report our experience in the management of uveitic cystoid macular oedema (CME) secondary to vemurafenib use.

Since October 2013, we have managed four cases of uveitis secondary to vemurafenib therapy at two general uveitis referral centres, three of the patients presenting cystoid macular oedema (CME). All the patients were male with a median age of 52.5 [42–73] years, and median initial visual acuity was 20/30 [20/20–20/400]. The dosage of vemurafenib at onset of uveitis was 960 mg twice a day in one patient, 720 mg twice a day in two patients and 480 mg twice a day in one patient. Median duration of vemurafenib therapy before uveitis onset was 9.5 [4–29] months. Uveitis was bilateral in three of the four patients and was classified as non-granulomatous and anterior in all cases. Three patients were found to have CME on optical coherence tomography. In these cases, treatment consisted of topical steroids, together with bilateral intravitreal injection of dexamethasone implants in one, oral prednisone in another and bilateral sub-Tenon's injection of triamcinolone in the last case. Intraocular inflammation and CME resolved in all three cases. Median VA at the last follow-up visit was 20/20 [20/15–20/100]. Vemurafenib was stopped and reintroduced after resolution of the uveitis in all patients. Median follow-up after reintroduction of vemurafenib was 6.5 [2–8] months, and uveitis has not been observed to recur after reintroduction. Table 1 shows clinical features and outcomes of all four patients.

Until recently, treatment options for metastatic melanoma were almost nonexistent. This situation has dramatically changed with the introduction of

Table 1. Clinical characteristics and outcomes of patients.

Gender	Age	Duration of vemurafenib therapy (months)	Dose of vemurafenib (mg/h)	Eye	Symptoms	Visual acuity on admission	Type of uveitis and clinical findings	Cystoid macular oedema	Treatment	Visual acuity (last visit)	Outcome	Follow-up (months)
Male	42	4	720/12	Both eyes	Blurry vision and red eyes	20/20; 20/20	Anterior	No	Topical steroids	20/15; 20/20	Resolved	2
Male	73	29	960/12	Both eyes	Blurry vision and mild pain	20/200; 20/400	Anterior, Posterior synechiae	Yes	Topical steroids + intravitreal dexamethasone implant	20/100; 20/63	Resolved	5
Male	45	12	720/12	Left eye	Blurry vision	20/50	Anterior, Posterior synechiae	Yes	Topical steroids + oral prednisone	20/20	Resolved	8
Male	60	7	480/12	Both eyes	Blurry vision, red eyes and watering	20/30; 20/30	Anterior, Posterior synechiae	Yes	Topical steroids+ sub-Tenon triamcinolone	20/20; 20/20	Resolved	8