

Intravitreal VEGF levels in uveitis patients and treatment of uveitic macular oedema with intravitreal bevacizumab

K Weiss^{1,2}, I Steinbrugger¹, M Weger¹,
 N Ardjomand¹, R Maier¹, BJ Wegscheider¹,
 A Wedrich¹ and Y El-Shabravi^{1,2}

Abstract

Purpose Clinical data suggest a role for VEGF in uveitic cystoid macular oedema (CME), even though the data on intravitreal VEGF levels in these eyes is still inconclusive. We determined intravitreal VEGF levels and treated uveitis patients with intravitreal bevacizumab.

Methods Intravitreal VEGF levels were measured in eight uveitis patients and 10 controls using cytometric bead array technology. In 11 eyes of a second group of uveitis patients, CME was treated using 1.25 mg bevacizumab intravitreally.

Re-injections of bevacizumab were given in patients showing a transient positive effect, defined as an increase of the best-corrected vision of at least two lines on a snellen chart. Alternatively, triamcinolone was given in patients, not responding to bevacizumab.

Results Mean intravitreal VEGF concentration was 82.75 ± 171.71 pg/ml (\pm SD) (range, 0.0–502.1 pg/ml), and below the detection levels in controls. A significant reduction of retinal thickness was seen at weeks 2 ($P = 0.001$) and 4 ($P = 0.007$). A significant improvement in VA was seen at week 2 ($P = 0.02$). Patients presenting with a CME in baseline fluorescein-angiogram responded well towards bevacizumab treatment, unless an extensive leakage from the choroid or a leakage of the optic disk was detectable. In these patients, only intravitreally administered triamcinolone led to a reduction of the CME.

Conclusions Our data suggest that patients presenting with a diffuse leakage from the choroid in the fluorescein angiogram or an extensive leakage of the optic disk should be

treated with intravitreal triamcinolone, whereas in patients presenting only a cystoid macular oedema bevacizumab treatment seems like a good choice.

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Introduction

Cystoid macular oedema (CME) is a frequent complication in patients with intraocular inflammatory diseases, leading to a significant visual loss.^{1,2} Treatments include oral or periocular corticosteroids, sometimes given in combination with oral carbonic anhydrase inhibitors,³ immune-modulating drugs, such as anti-TNF- α therapy^{4–6} and intravitreally administered triamcinolone (TA).^{7,8}

Macular oedema in the setting of uveitis, as also for diseases, such as diabetic retinopathy or retinal vein occlusions (RVOs), arises due to a disruption of the blood–retinal barrier, with consecutive exudation and accumulation of serous fluid.⁹ Evidence exists that VEGF is not only involved in the pathogenesis of CME in diabetes, RVO, but also in intraocular inflammatory diseases. Firstly, VEGF is 50 000 times more potent than histamine in inducing vascular permeability,¹⁰ and secondly, in experimental autoimmune uveitis (EAU), the expression of VEGF is markedly increased in the retina.¹¹ In human uveitic eyes, the role of VEGF is, however, not yet clearly defined. Fine *et al*¹² found increased VEGF concentrations in the aqueous humour of uveitis patients who

¹Department of Ophthalmology, Medical University of Graz, Austria

²Department of Ophthalmology, General Hospital Klagenfurt, Austria

Correspondence: Y El-Shabravi, Department of Ophthalmology, General Hospital Klagenfurt, St Veiterstraße 43, A – 9020 Klagenfurt, Austria
 Tel: +43 463 538 24203;
 Fax: +43 463 538 23194.
 E-mail: yosuf.elshabravi@meduni-graz.at

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presented with CME, when compared with those without macular oedema. A follow-up study by Banerjee *et al*¹³ was, however, unable to detect VEGF in the vitreous of uveitic eyes.

Clinical data, such as resolution rates of the uveitic macular oedema following anti-VEGF treatment, vary between the previously published studies.^{14–16} All studies used bevacizumab, a humanized monoclonal antibody that targets VEGF. Cordero Coma *et al*¹⁵ who treated 13 eyes of 13 patients found an improvement of vision in 62% of his patients after a single dose of bevacizumab. A second study carried out by Ziemssen *et al*¹⁴ observed only a transient and very limited effect in three out of six patients after bevacizumab treatment, and the most recent study by Mackensen *et al*¹⁶ described a positive effect of treatment in 72% of 10 patients. The differences in the treatment response seen could neither be addressed to the dosage used, 2.5 *vs* 1.25 mg, nor the time between the occurrence of the macular oedema and intravitreal bevacizumab treatment. To rationally decide the amounts of anti-VEGF treatment needed in uveitic CME, it is necessary to know the intraocular levels achieved in uveitic eyes. So far, as only conflicting data on intraocular VEGF in uveitis patients exist,^{12,13} we first measured intravitreal VEGF in vitreous samples of eight uveitis patients. A second aspect of the study was to include fluorescein angiogram (FA) as a possible tool in distinguishing patients responding *vs* patients lacking a response towards bevacizumab treatment. Finally, we compared the effect of bevacizumab to that of TA in uveitic CME non-responding towards bevacizumab after the first injection.

Materials and methods

Evaluation of intravitreal VEGF levels

To determine vitreous VEGF concentration among uveitis patients, we measured VEGF levels using

cytometric bead array technology (CBA) in eight uveitis patients and 10 control subjects. (Table 1) Control subjects were treated for the presence of an epiretinal membrane or a macular hole. Four of the uveitis patients were vitrectomized for the presence of an intensive vitreous infiltration obscuring the visibility of the posterior pole. The remaining four patients showed a vitreomacular traction syndrome (VTMS) associated with an epiretinal membrane.

Undiluted vitreous samples were obtained during a standard three-port pars plana vitrectomy at the beginning of the surgery. The obtained specimen was immediately transferred into a sterile plastic tube on ice. Subsequently, the sample was centrifuged at 5000 r.p.m. for 10 min, aliquoted and stored at -70°C until assayed.

The concentration of VEGF was determined in the vitreous samples using the BDTM CBA Flex Set System, BDTM Human Soluble Protein Master Puffer Kit (Cat. no. 558246, BD Bioscience-Pharmingen, San Diego, CA, USA) and the BD™ CBA Flex Set for VEGF measurement (Cat. no. 558336, BD Bioscience-Pharmingen). Measurements were performed according to the manufacturers protocol and as described previously.¹⁷ In brief, The BD™ CBA Flex Set contains a bead population with distinct fluorescence intensity as well as the appropriate phycoerythrin (PE) detection reagent and standard. The bead population is coated with capture antibodies specific to VEGF. As previously described,¹⁷ the bead population was incubated with recombinant standards or test samples to form sandwich complexes. After the addition of PE-conjugated detection antibodies, the samples were incubated again and then resolved in the FL-3 channel of an FACSCalibur flow cytometer (BD Bioscience-Pharmingen). The results were generated in graphic and tabular format by using the CBA analysis software (BD Bioscience-Pharmingen).

Table 1 Patient data, uveitis entities, current therapy, and concentrations of vascular endothelial growth factor (VEGF) in vitreous of group 1

Patient	Age	Gender	Diagnosis	Current treatment	VEGF in pg/ml in vitreous
1	46	F	Herpes retinitis	Oral corticosteroids 25 mg/day for 1 week, acyclovir	34.08
2	69	F	Gliose, CME, disseminated Chorioretinitis	Oral corticosteroids 5 mg/day for >6 months	3.88
3	39	M	Chronic iritis, no CME	Local corticosteroids	0.00
4	11	M	Uveitis intermedia, CME	Local, corticosteroids	502.10
5	79	F	Uveitis intermedia, epiretinal membrane, CME	Oral corticosteroids 5 mg/day for 28 months	33.35
6	41	F	chronic uveitis antibody, CME	Oral corticosteroids 7.5 mg for 24 months	6.49
7	72	M	Chronic iritis, no CME	Acyclovir, local corticosteroids	0.00
8	7	M	JIA-associated uveitis, CME,	MMF 2 g/day, MTX 10 mg/week, oral corticosteroids 2.5 mg for 6 months	82.11
					Mean 82.75

Mean 82.75 pg/ml (SD \pm 171.71 pg/ml).

Intravitreal anti-VEGF treatment

A second group comprised of 11 eyes of nine uveitis patients (Table 2; five women and four men) with continued loss of vision associated with cystoid macular oedema were treated with intravitreal injections of 1.25 mg bevacizumab. Three of the patients were treated with systemic immune modulatory medication for a minimum of 6 months before intravitreal bevacizumab treatment. Infliximab was given at a dose of 5 mg/kg/body weight every 6 weeks to patients 2 and 3, azathioprine was given at a dose of 2 mg/kg/body weight per day to patient 2, and mycophenolate mofetil was given at dose of 2 g per day to patient 3. Methotrexate was given at a dose of 20 mg once weekly to patient 7 and 15 mg once weekly to patient 9.

No patient from the vitrectomy group, described above, has been included into the bevacizumab treatment group, as performing a vitrectomy alone has already been reported to have a positive influence on the inflammatory macular oedema.¹⁸

All patients were informed of potential benefits and side effects. The experimental nature of analyses was approved by the local ethics commission. Informed consent was given by all subjects. CME was verified by fundus examination, FA, and OCT scanning. FA was performed at baseline and 4 weeks after bevacizumab treatment. Visual acuity testing and measurements of central retinal thickness, using OCT were performed at

baseline, weeks 1, 2, and 4. After a minimum of 4 weeks, retreatment with 1.25 mg of bevacizumab was performed in eyes showing a transient positive response after the first bevacizumab injection, which was defined as an increase of at least two lines on the snellen chart. Patients lacking a positive response after intravitreal bevacizumab treatment defined as mentioned above were treated with 4 mg of intravitreal TA.

Statistical analyses were performed using a two-tailed, paired *t*-test, as described previously.¹⁶ A *P*-value of <0.05 was considered statistically significant. For statistical evaluation, the visual acuity was converted from snellen into LogMar as described previously.¹⁶

Results

Results on intraocular VEGF levels

To obtain a rationale for the amounts of bevacizumab to be injected, we first measured intravitreal VEGF levels in eight uveitis patients and 10 control subjects. Patient data and uveitis entities, current therapy, and VEGF levels are presented in Table 1. The mean concentration of VEGF measured in our uveitis patients was 82.75 pg/ml ± 171.71 (± SD) (range, 0–502.1 pg/ml). In the control group, VEGF was below the detection levels in all subjects. For comparison, in samples of our patients with diabetes, the mean intravitreal VEGF concentration was 954.98 pg/ml (range, 10–1325 pg/ml; Maier *et al*¹⁹).

Table 2 Patient data, uveitis entities, and concurrent treatment from the second group treated with intravitreal bevacizumab and/or triamcinolone

Eye no.	Age	Gender	Diagnosis	Therapy at the time of treatment	Macular oedema	Duration of the CME
1	46	F	HLA B27 + AAU	Local corticosteroids q4d for 8 months	CME	3 months
2	53	F	Birdshot chorioretinitis	Infliximab 5 mg/kg/BWQ 6 weeks for > 1 a, 100 mg/day AZT, oral corticosteroids 5 mg/day	Diffuse leakage from the choroid and the optic disks	20 months
3	45	F	Retinal vasculitis	Infliximab 5 mg/kg/BWQ 6 weeks for > 1 a, mycophenolate mofetil 2g/day	Diffuse leakage from the choroid and the optic disks	12 months
4	48	F	Subacute anterior uveitis	TA parabulbar injection (1) 3 months before baseline	Diffuse leakage from the choroid and the optic disks	4 months
5a	58	M	HLA B27-AAU	No treatment for > 3 months	CME	2 months
5b	58	M	HLA B27-AAU	No treatment for > 3 months	CME	1 month
6a	40	M	Intermediate uveitis	No treatment for > 3 months	CME, leakage of the optic disk	7 months
6b	40	M	Intermediate uveitis	No treatment for > 3 months	CME, leakage of the optic disk	7 months
7	48	M	HLA B27 + AAU	20 mg/week MTX for 2 months	CME	2 months
8	31	M	HLA B27 + AAU	Local corticosteroids q2d for 2 months	CME	2 months
9	49	F	HLA B27- AAU	15 mg/kg/week MTX > 12 months	CME	1 month

AAU = acute anterior uveitis; bev. = bevacizumab; CME = cystoid macular oedema; F = female; HLA = human leukocyte antigen; M = male; TA = triamcinolone; MTX = methotrexate; AZT = azathioprine. 5a is the right eye, 5b is the left eye of one patient. 6a is the right eye, and 6b is the left eye of one patient.

Data published on intravitreal VEGF levels among patients with exudative age-related macular degeneration (AMD) were below 64 pg/ml.

Owing to the fact that the intravitreal VEGF levels we found in our uveitis patients were comparable with those seen in case of AMD patients, we decided to use 1.25 mg bevacizumab, the amount usually used in patients with exudative AMD.

Results of intravitreal anti-VEGF treatment

The second group comprised of 11 eyes of 9 patients were treated with 1.25 mg bevacizumab. Patient data, uveitis

entities, and concurrent treatment are shown in Table 2. The mean age was 46.4 SD ± 7.7 years (range, 31–58). Data on visual acuity is presented in Table 3. Central retinal thickness as measured by OCT is shown in Table 4. The presence of fluorescein leakage of the optic disk was seen at a very low level in six out of eleven eyes (Figure 1), where as an extensive leakage of the macula was found in four eyes (patients 2, 3, 4, and 6a (6a is the right eye); Figure 2). An extensive diffuse leakage from the choroid, as shown in Figure 3, suggesting an extensive alteration of the outer blood–retinal barrier was seen in three eyes (patients 2, 3, and 4). The visual acuity changes after 2 weeks were statistically significant

Table 3 Visual acuity (VA) in LogMar from patients treated with bevacizumab, and retreatment with bevacizumab and triamcinolone (TA)

Eye no.	VA before treatment	VA after 1 week	VA after 2 weeks	VA after 4 weeks	Number of bevacizumab injection	Number of TA injection	VA before re-treatment	Best vision after re-treatment	Best result after re-treatment ^a
1	0.6	0.4	0.2	0.5	2		0.5	0.2	3
2	1.0	1.0	1.0	1.0	1				
3	0.3	0.3	0.5	0.5	1	1	0.7	0.1 ^b	6
4	0.4	0.2	0.5	0.7	1	1	0.7	0.3	4
5a	0.4	0.2	0.2	0.1	2		0.6	0.2	5
5b	0.3	0.1	0.0	0.0	2		0.7	0.0	7
6a	0.2	0.2	0.1	0.6	1				
6b	0.4	0.1	0.1	0.2	1				
7	0.6	0.5	0.3	0.5	2		0.5	0.3	4
8	0.2	0.1	0.1	0.0	2		0.1	0.0	1
9	0.2	0.0	0.0	0.0	2		0.0	0.0	1
Mean	0.42	0.28	0.27	0.37			0.59	0.23	

^aBest result after re-treatment compared to vision before the second treatment in lines.

^bCataract surgery has been performed due to the lack of an adequate visibility of the fundus.

Table 4 Central retinal thickness in μm

Eye no.	Retinal thickness before treatment	Retinal thickness after 1 week	Retinal thickness after 2 weeks	Retinal thickness after 4 weeks	Number of AV injection	Number of TA injection	Retinal thickness before re-treatment	Retinal thickness 4 weeks after re-treatment
1	739	490	500	500	2		589	507
2	622	481	639	597	1			
3	598	415	450	500	1	1	437	290
4	614	^a	523	647	1	1	647	340
5a	423	^a	^a	332	2			323
5b	531	348	340	357	2		598	340
6a	630	439	514	681	1			
6b	689	572	675	599	1			
7	647	415	481	497	2		497	515
8	464	464	431	423	2		423	381
9	497	315	323	298	2		298	298
Mean	586.7	437.7	487.6	493.7			568.1	389.8
	SD ± 97.10	SD ± 77.03	SD ± 112.39	SD ± 129.83			SD ± 122.35	SD ± 88.93

TA = triamcinolone.

A reduction of the retinal thickness was seen in all eyes after the first or second week.

^aOCT not performed.

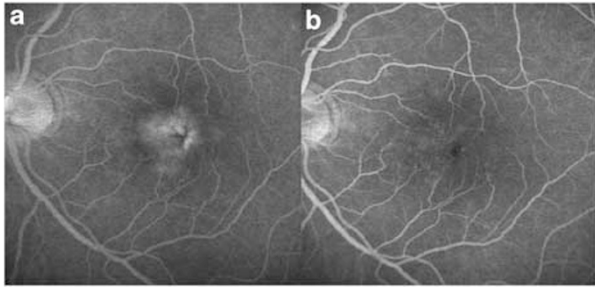


Figure 1 Late phase of the fluorescein angiogram at base line and 4 weeks after treatment with 1.25 mg bevacizumab: Eyes presenting only with a cystoid macular oedema (a) responded well (b) towards intravitreal bevacizumab treatment; for example, the eye 6b (the left eye of the patient) showing an increase in visual acuity by three lines and a reduction of retinal thickness seen using OCT at week 4 after the bevacizumab injection.

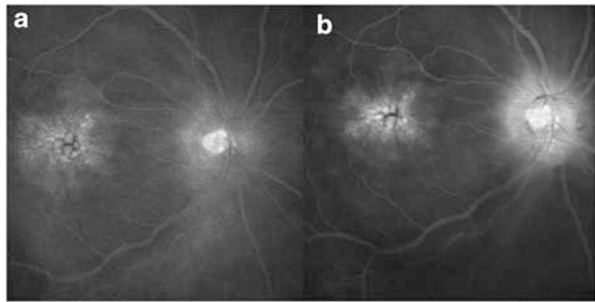


Figure 2 There was no effect of intravitreal bevacizumab treatment at week 4 in eyes with an extensive leakage of choroid and the optic disk (a) seen in the fluorescein angiogram (b); for example, patient 4 presented with a diffuse leakage from the choroid accompanied by an extensive fluorescein leakage of the optic disk. The patient lost one line in VA after 2 weeks despite bevacizumab therapy. Treatment with triamcinolone, on the other hand, could raise the VA from 20/100 to 20/40.

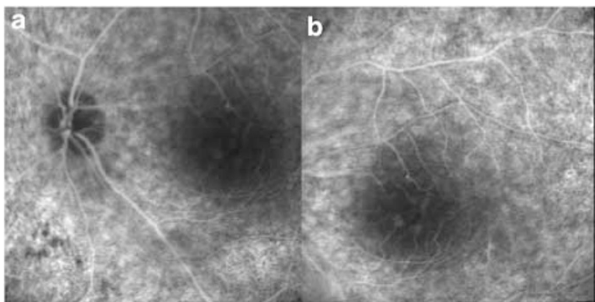


Figure 3 Diffuse leakage due to changes in the outer retinal-blood barrier (a) showed no change in fluorescein angiogram 4 weeks after bevacizumab (b). OCT showed a reduction of retinal thickness, but patient 3 had a loss of two lines in VA. Treatment with triamcinolone had a positive effect, the VA raised from 20/100 to 20/25 (intermediate cataract surgery) and led to a reduction of retinal thickness from 437 to 290 μm after 4 weeks.

($P = 0.02$). An improvement of visual acuity was seen in nine out of eleven eyes at week 1 or 2. Compared to week 1 or two, seven of these nine eyes lost at least one line within the following 2 weeks.

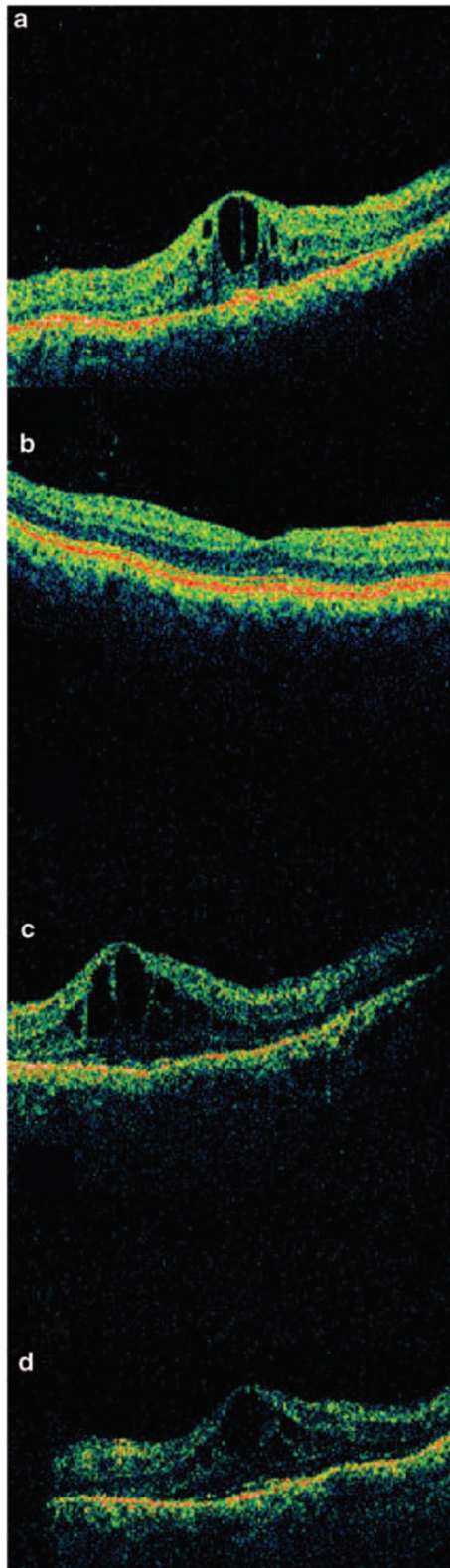
Thus, at week 4, even though seven eyes still showed an improvement in vision when compared to baseline, only three eyes remained at their best visual acuity achieved after bevacizumab treatment, suggesting that the effect of intravitreal bevacizumab is only transient in most patients treated, as already described.^{14–16}

A reduction of retinal thickness was seen in all eyes in week 1 or 2. The mean retinal thickness, as measured by OCT, was $586.7 \pm 97 \mu\text{m}$ before bevacizumab treatment. After 1 week, the mean retinal thickness was $437.7 \pm 77 \mu\text{m}$, and it was 487.7 ± 112 and $493.7 \pm 129 \mu\text{m}$ at weeks 2 and 4, respectively. The reduction of retinal thickness was statistically significant comparing baseline to weeks 2 ($P = 0.001$) and 4 ($P = 0.007$). Retreatment with bevacizumab was performed in six eyes, at week 4 after the first injection. Data are presented in Tables 3 and 4. One patient (patient 6) refused any additional intravitreal treatment, using either bevacizumab or TA, which was given alternatively in patients lacking an effect of bevacizumab treatment. In these patients, intravitreal TA was very effective in reducing the CME (Tables 3, 4). OCT pictures are shown in Figure 4. One patient (patient 2) received one intravitreal injection of TA into the contralateral eye that has been treated with bevacizumab. The TA-treated eye showed an improvement of visual acuity from 20/800 to 20/200, the bevacizumab-treated eye remained at a visual acuity of 20/200. Intravitreal TA resulted in intraocular pressure raise above 35 mmHg; thus, the patient has not been retreated with TA despite the lack of an effect of intravitreal bevacizumab (data shown in Tables 3, 4). Retreating patients showing a transient improvement in their visual acuity with one bevacizumab injection lead to similar improvement of their visual acuity after the second injection. The retinal thickness reduction seen in OCT improved from a mean of $568.1 \pm 122.35 \mu\text{m}$ to a mean of $389.8 \pm 88.93 \mu\text{m}$ ($P = 0.03$). Indicating that the retreatment is at least as successful as the first injection in eyes showing a positive response after the first injection.

Conclusions

We have treated 11 eyes in nine uveitis patients for their CME with 1.25 mg intravitreal bevacizumab. The dose of 1.25 mg was used, as intraocular VEGF levels that we detected in the vitreous of uveitis patients were similar to those described in patients with adult macular degeneration, where 1.25 mg is the most commonly used dosage.²⁰

We found a positive response to intraocular bevacizumab treatment only in eyes with limited macular and/or optic disk leakage in the FA (Figure 1),



recapitulating the positive response of the patient, whose FA is presented by Cordero Coma *et al.*¹⁵ Eyes showing an extensive fluorescein leakage from the choroid and the optic disks (Figures 2 and 3) did not respond with an increase in visual acuity following bevacizumab treatment. In these eyes, only intravitreal TA was able to induce an increase in vision, suggesting that in eyes with diffuse fluorescein leakage from the choroid TA rather than bevacizumab might be the treatment of choice. A possible explanation for the superiority of TA over bevacizumab in these eyes might be, that depending on the type of pathological condition causing the oedema and the stage of the uveitis, the relative contributions of different vascular permeability-enhancing mediators may vary and other factors, such as cytokines²¹ or metalloproteinases,²² may play a more prominent role. An alternative treatment option to intravitreal TA might be the use of a combined treatment modality by (a) blocking the effect of intraocular VEGF released in case of an intraocular inflammation using bevacizumab and (b) a modification of the systemic treatment, using for instance of biologics, such TNF- α -blocking antibodies, to maintain the uveitis under control and block, if possible, the effects of cytokines and/or metalloproteinases.

The positive effect of both intravitreal bevacizumab as well as TA was only transient. Even though nine eyes showed a gain in vision of at least two lines on the snellen chart in the first 2 weeks, in only three eyes, this gain of vision was sustained over the follow-up period. The fact that eyes responding with an increase of at least two lines on the snellen chart after the first injection, responded to the retreatment with a comparable gain of vision, indicate that the effect of bevacizumab is repeatable.

In conclusion, we found a positive effect of bevacizumab treatment in uveitic macular oedema in eyes lacking an extensive breakdown of the outer blood-retinal barrier or an extensive leakage of optic disk as seen in the FA. In these patients, intravitreal TA seems to be the better treatment option. A major limitation of our study is the small number of patients included, thus larger studies are warranted.

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Figure 4 Treatment with triamcinolone compared with bevacizumab in eyes with extensive diffuse leakage and/or leakage of the optic disk in FA. Patient 3 showed a good response towards treatment with triamcinolone. After 4 weeks, the retinal thickness was reduced from 647 μm (a) to 340 μm (b), and the VA raised from 20/100 to 20/40 bevacizumab treatment in this patient had almost no effect and the patient lost two lines in VA. The retinal thickness before (c) and after 4 weeks of intravitreal bevacizumab injection (d).

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