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RESEARCH ARTICLE

Long-term Efficacy of TNF-alpha Inhibitors on Persistent Uveitic Macular Edema: A Swiss Multicenter Cohort Study

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ABSTRACT

Purpose: To assess the efficacy of tumor necrosis factor-alpha inhibitors (TNFi) on uveitic macular edema (ME) unresponsive to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

Methods: This multicenter retrospective study included patients with uveitic ME persisting despite csDMARDs. The effect of an additional TNFi on central retinal thickness (CRT), best corrected visual acuity (BCVA) and corticosteroid need was evaluated.

Results: Thirty-five eyes (26 patients, mean age 42.9 ± 15.2 years) were included. CRT decreased from 425 ± 137 µm to 294 ± 66 µm ($p < .001$) and 280 ± 48 µm ($p < .001$) at 1 and 4 years of follow-up, respectively. BCVA improved from 0.28 ± 0.22 to 0.21 ± 0.48 (1 year, $p = .013$) and 0.08 ± 0.13 logMAR (4 years, $p = .002$). The proportion of patients requiring systemic corticosteroids decreased from 88.5% to 34.8% (1 year) and 15.4% (4 years).

Conclusion: The addition of a TNFi resulted in an improvement of CRT and BCVA for up to 4 years in uveitic ME but rescue treatments were needed for some patients.

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Adalimumab; infliximab; uveitis; macular edema; TNF-alpha inhibitors

Uveitis comprises a heterogeneous group of intraocular inflammatory diseases and is idiopathic in approximately half of patients.[1,2] In case of a chronic or recurrent course, it results in debilitating complications, potentially leading to severe and possibly permanent visual impairment.[3] Besides anterior segment complications, such as cataract, glaucoma and band keratopathy, also retinal complications, such as uveitic macular edema (ME), secondary epiretinal gliosis, retinal vascular occlusion and/or retinal detachment, have been reported.[3,4] Uveitic ME is defined as an increase of central retinal thickness (CRT) due to accumulation of intra- and extracellular fluid as a consequence of an inflammatory breakdown of the inner and/or outer blood-retina barriers (i.e., increased permeability of the retinal pigment epithelium and retinal vasculature, especially leaking of perifoveal capillaries).[5] Prevention of ME, its early detection and efficacious treatment is a prerequisite for preventing structural damage to the foveal center and for improving the long-term functional outcome in these patients.[6] After excluding an infectious etiology, an anti-inflammatory treatment strategy is employed for the treatment of uveitic ME, with the aim of controlling the underlying inflammation and thereby reconstituting the blood-retinal and blood-aqueous barriers.[7] The first-line treatment consists mainly of corticosteroids, applied systemically or eventually locally as peri- or intravitreal injections or intravitreal implants,[7,8] while topical nonsteroidal anti-inflammatory drugs (NSAIDs) have only a limited additive effect.[5] Recurrent or chronic ME, as well as bilateral occurrence, require a long-term treatment strategy to prevent permanent disability.[5] To spare corticosteroids and prevent the associated adverse effects, the use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as the antimetabolites methotrexate, azathioprine, mycophenolate mofetil or sulfasalazine, and the calcineurin inhibitor cyclosporine A has been established.[5] If remission, defined as visual recovery in the absence of inflammatory activity over at least 3 months (according to the Standardization of uveitis nomenclature for reporting clinical data (SUN) classification),[9] is not achieved with decreasing corticosteroid doses and csDMARDs, biologic agents are considered as third-line therapy. In addition to this indication, the TNFi adalimumab (ADA) has also been approved by many national medical agencies, including the FDA and EMA, as a second-line option if corticosteroids fail to completely control uveitis activity.[10,11] The rationale for its use is the detection of high concentrations of TNF-alpha, a proinflammatory cytokine, in the aqueous humor and also frequently in the sera of patients with endogenous uveitis and other systemic noninfectious inflammatory conditions.[12]

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Retrospective case-series, studies and the large prospective VISUAL 1 and 2 trials have demonstrated a significant improvement of inflammation and the associated ME. However, the follow-up of these studies is limited to 2 years.[13–15]

The aim of this retrospective multicenter cohort study was to investigate the efficacy of TNFi treatment on persisting and treatment-refractory uveitic ME up to 4 years in a real-life setting.

Methods

Study design and patients

This retrospective cohort study was performed at five tertiary uveitis referral centers in Switzerland (Department of Ophthalmology, Bern University Hospital, Inselspital, Bern; Berner Augenklinik am Lindenhofspital, Bern; Department Ophthalmology, University Hospital Zurich, Zurich; Jules-Gonin Eye Hospital, Department of Ophthalmology, University of Lausanne, Lausanne; Department of Ophthalmology, University of Basel, Basel). Patients with noninfectious uveitis, an age of ≥18 years and chronic ME (CRT > 300 µm) despite corticosteroid and/or csDMARD treatment with a baseline visit between 2006 and 2017 were identified with a systematic search in all study centers and were included if they had been followed for a minimum of 6 months after addition of ADA or IFX. The last follow-up visit was in 2020. The selection of ADA or IFX was at the discretion of the treating ophthalmologists and rheumatologists at each study center. Patients who had undergone intraocular surgery within 6 months prior to baseline or had been treated with any biological drug before baseline were excluded. The follow-up was censored at time-point of TNFi discontinuation. The study conformed to the Declaration of Helsinki and was approved by the local regulatory authorities (Kantonale Ethikkommission Bern, ID #2017-01992, Ethikkommission Nordwest-und Zentralschweiz, Ethikkommission Zürich, Commission cantonale d'éthique de la recherche sur l'être humain CER-VD). The study was conducted with the general consent of the patients to use their coded data.

Data collection

Clinical data and optical coherence tomography (OCT) findings were retrospectively extracted from the electronic medical records of patients of the participating hospitals. Baseline parameters included demographic information (age, sex, and ethnicity), anatomic location of the uveitis according to the SUN classification,[9] laterality of uveitis and associated systemic diseases. The following clinical findings were documented: best corrected visual acuity (BCVA; Snellen chart units were converted to logMar for statistical analysis) and retinal thickness in the central 1 mm area centered to the fovea (foveal CRT). CRT measurements were based on horizontal line scans through the foveal center and quantified on a micrometer scale from the inner retinal surface to Bruch's membrane, where this was visible or presumed to be if not visible, using Spectralis™ (Heidelberg Instruments, Heidelberg, Germany), Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) or SOCT Copernicus (Reichert/Optopol Technology, Inc, Depew, NY). Since the CRT values of different OCT machines are quantitatively not directly comparable, a correction index was applied to allow for their comparison.[16,17] Given the low intraclass correlation of 0.09 on our primary outcome (CRT), the dependency of the nine pairs of eyes in this series accounted for only 9% of the variance. Therefore, we decided to include both eyes of a patient if bilateral macular involvement was present at baseline but not to account for the dependency of both eyes from the same patient in the calculations.[18] Any intercurrent uveitis flare was registered for each time juncture. Data pertaining to the local and systemic anti-inflammatory therapies and their changes, including the reasons for treatment adaptation before baseline and after addition of a TNFi were recorded along with the need for rescue therapy (systemic corticosteroid pulse therapy with increase in the daily prednisone equivalent dose to ≥1 mg per kg of body weight, intravitreal corticosteroid injections or implants). Due to the retrospective nature of this study, a window of tolerance for the predefined clinical follow-up visits was set (i.e., at −3 ± 1 months; baseline (= beginning of TNFi treatment); +3 ± 1, +6 ± 1, +9 ± 1, +12 ± 1 months; and thereafter annually (± 3 months).

Outcome measures

The primary outcome was defined as the change in CRT in response to the initiation of TNFi treatment. Secondary outcomes included change in BCVA, corticosteroid-sparing effect and change in csDMARD co-therapy. Treatment failure was defined as the absence of an impact of a TNFi on CRT, triggering the switch to another biologic agent, with a flare-up of uveitis requiring any rescue therapy (as defined above) beyond 3 months after baseline.

Statistical analysis

In this longitudinal study, Friedman's test was applied to analyze the changes of CRT and BCVA over time. Since multiple comparisons increase the risk of introducing type I error, the significance level was adjusted using the Holm's correction, which is a sequentially rejective Bonferroni test that progressively adapts the threshold for rejecting the null hypothesis. This correction is less conservative compared to the Bonferroni correction, which leads to a higher risk for type II error.[19] To control for type I errors, but at the same time without drastically driving up type II errors, Holm's correction offers a good solution.[20,21] All statistical evaluations were performed using the SPSS software package V.27 (SPSS, Inc., Chicago, Illinois, USA), with the level of significance being set at $p < .05$. Data are presented as means ± standard deviations (SDs) and medians with interquartile ranges (IQRs). For CRT and BCVA, missing data were substituted according to the last observation carried forward (LOCF) method to assess the impact of the missing values.[22]

Results

A total of 26 patients (mean age 42.9 ± 15.2 years; 42.3% females) with uveitic ME (35 eyes) were included in this study. The mean uveitis duration before initiation of TNFi therapy was 2.9 ± 4.2 years. ME was bilateral in nine patients (34.6%). Uveitis localization, etiology and course are displayed in Table 1. The majority of patients (n = 19 patients, 73.1%; n = 28 eyes, 80%) presented with intermediate uveitis. Uveitis

Table 1. Uveitis localization, type and course of patients (n = 26) with persistent macular edema (ME).

	Patients, N (%)	Eyes with ME, N (%)
Uveitis localization		
Intermediate uveitis	19(73.1)	28(80)
Anterior uveitis	3(11.5)	3(8.6)
Posterior and panuveitis	2(7.7)	2(5.7)
Idiopathic retinal vasculitis	2(7.7)	2(5.7)
Uveitis etiology/associated disease		
Idiopathic uveitis	14(53.8)	21(60)
Sarcoidosis	4(15.4)	5(14.3)
HLA-B27 positive spondylarthritis	5(19.2)	5(14.3)
Behçet's disease	2(7.7)	3(8.6)
Inflammatory bowel disease	1(3.8)	1(2.9)
Course of uveitis		
Recurrent	6(23.1)	7(20.0)
Chronic	20(76.9)	28(80.0)

was mainly idiopathic (n = 14 patients, 53.8%; n = 21 eyes, 60%). All three patients (11.5%) with anterior uveitis were HLA-B27 positive. Twenty patients (76.9%) suffered from a chronic uveitis course. The mean uveitis duration prior to TNFi treatment initiation was 2.9 ± 4.2 years (median 1.4, IQR 0.7 to 2.5 years) (Table 2).

All but one patient (96.2%) received TNFi therapy for a minimum of 1 year, 76.9% (n = 20) for 2 years, 73.1% (n = 19) for 3 years and 50% (n = 13) for 4 years, respectively (Table 3, Figure 1). The mean follow-up of patients under TNFi treatment was 3.0 years (median 3.5, SD 1.3, IQR 2.25 to 4). In patients with ADA as their first TNFi, the subcutaneous application of a standard dosage of 40 mg was given every second week in all 14 patients. In two patients the interval was extended to 3 weeks after a treatment duration of 1 and 3 years, respectively. For patients in the IFX group, a dosage of 3–5 mg/kg body weight was given at discretion of the treating ophthalmologist and rheumatologist. Mean dosage was 375 mg (median: 400 mg, SD: 135 mg, IQR 300 mg to 400 mg). The first two dosages were usually separated by two weeks and after that a four-week interval was established. In 10 out of 12 patients (83.3%) with IFX the interval was extended to 6, 8, 10 and even 12 weeks after a mean of 12.3 months (10 patients), 23.6 months (7 patients), 32 months (3 patients) and 36 months (1 patient) of treatment duration.

A total of 15 out of 26 patients (57.7%) were treated with a csDMARD before baseline, beyond these methotrexate (n = 9), azathioprine (n = 2), cyclosporine A (n = 1), azathioprine & cyclosporine A (n = 2) and methotrexate & cyclosporine A (1 patient). Under TNFi treatment, a total of 22 patients (84.6%) received concomitant csDMARD treatment, including methotrexate (n = 13), azathioprine (n = 4), cyclosporine A (n = 1), and leflunomide (n = 1), whereas 3 patients received two different csDMARDs (n = 2 cyclosporine, which was switched to methotrexate; n = 1 methotrexate, which was switched to mycophenolate mofetil). The most relevant change at baseline was the addition of methotrexate in 5 patients. The addition of low dose methotrexate belongs to the standard of care in part of the centers to prevent the formation of anti-drug antibodies but was not triggered by disease activity.

Table 3. Patients with ongoing TNFi treatment at different follow-up time points.

	Patients taking a TNFi (N/%)	Patients lost to follow-up (N/%)
3 months	26 (100%)	
6 months	26 (100%)	
9 months	25 (96.2%)	
1 year	25 (96.2%)	
2 years	20 (76.9%)	
3 years	19 (73.1%)	
4 years	13 (50.0%)	5 (19.2%)

Table 4 shows the reasons for discontinuation or switch from the first introduced TNFi. A total of 10 of our patients (38.5%) remained under treatment with the initial TNFi for the whole follow-up period. The remaining patients discontinued the treatment (n = 8; six of them due to remission) or switched treatment to another TNFi (three patients from ADA to IFX and three patients from IFX to ADA). In one patient, treatment was temporarily interrupted, and in another patient, TNFi therapy was switched from ADA to IFX and stopped thereafter. All 26 patients started TNFi therapy because of uveitis activity with persisting ME (14 patients started on ADA [53.8%] and 12 patients started on IFX [46.2%]). After exclusion of suggestive lesions at baseline in none of our patients any demyelinating CNS lesions were observed under TNFi treatment.

Mean CRT was 435 µm in patients receiving ADA (SD 149um, IQR 327 to 480) and 414 µm in IFX (SD 127um, IQR 337um to 467um), respectively (p = .81). CRT was significantly reduced at all follow-up time points compared to baseline (Figure 2) ($p < .008$). It decreased in the first year of TNFi therapy by 31% (baseline: 425 ± 137 µm; median 391 µm, IQR: 332 to 474 µm; year 1: 294 ± 66 µm; median 277 µm, IQR: 251 to 335 µm; $p < .001$) and further by a total of 34% after 4 years (year 4: 280 ± 48 µm; median 259 µm, IQR: 243 to 310 µm; $p < .001$). The results remained widely unchanged after applying the LOCF method (data not shown). At the 4-year follow-up, 13 eyes (72.2%) in nine patients (69.2% of all patients still under TNFi treatment) had a CRT < 300 µm and/or a reduction of initial CRT > 30%. BCVA improved after the start of TNFi treatment from 0.28 ± 0.22 logMar (median 0.22, IQR: 0.10 to 0.40) at baseline to 0.21 ± 0.48 logMar (median 0.00, IQR: 0.00 to 0.21; $p = .013$) after 1 year and further to 0.08 ± 0.13 logMar after 4 years (median 0.00, IQR: 0.00 to 0.22;

Table 2. Demographic data and baseline characteristics.

Patients, n = 26	
Age at uveitis manifestation, years, mean ± SD	40.0±15.4
Age at TNFi start, years, mean ± SD	42.9±15.2
Uveitis duration at TNFi start, years, mean ± SD	2.9±4.2
Female sex, N (%)	11(42.3%)
Eyes, n = 35	
BCVA at baseline, LogMar, mean ± SD	0.28 ± 0.22 (median 0.22, IQR: 0.10 to 0.40)
CRT at baseline, µm, mean ± SD	425 ± 137 (median 391, IQR: 326 to 481)

BCVA: Best corrected visual acuity; CRT: Central retinal thickness; IQR: 25% and 75% interquartile range; SD: standard deviation.

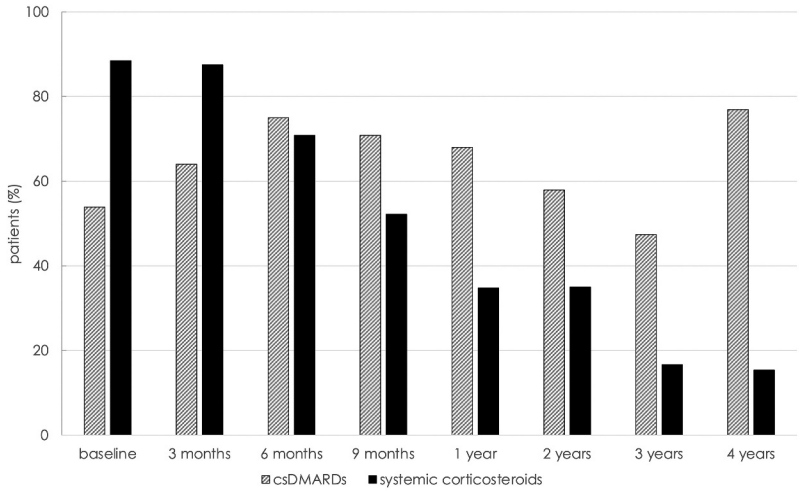

Figure 1. Percentage of patients on TNFi therapy with additional conventional synthetic DMARDs (csDMARD) and/or systemic corticosteroids.

Table 4. Adherence to TNFi treatment (ADA = Adalimumab; IFX = infliximab) and reasons for discontinuation during the 4 year follow-up (n = 26 patients). n. a. = not applicable.

Adherence to TNFi treatment	Reasons for TNFi stop/switch
10 patients under continuous TNFi treatment (ADA n = 4; IFX n = 6)	n. a.
Six patients switched from ADA to IFX (n = 3) or IFX to ADA (n = 3)	Insufficient effect on uveitis (n = 5)
	Adverse events (n = 1)
One patient paused and re-initiated later (ADA)	Uveitis recurrence after remission (n = 1)
One patient switched from ADA to IFX and stopped	Insufficient effect on associated disease (n = 1)
Eight patients discontinued TNFi therapy (ADA n = 5; IFX n = 3)	Remission of uveitis (n = 6)
	Adverse events (n = 1)
	Unknown (n = 1)

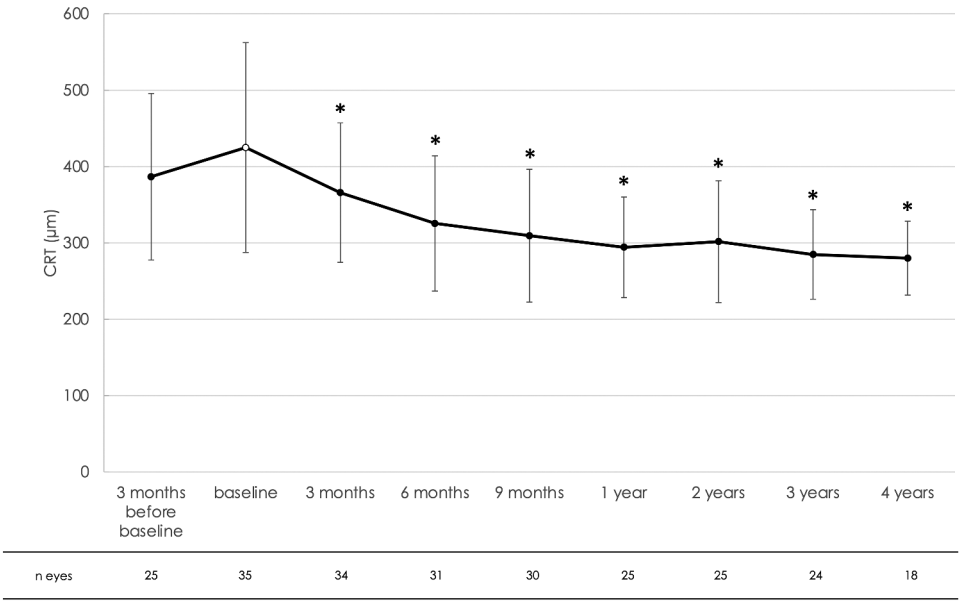

Figure 2. Mean central retinal thickness (CRT) of patients on TNFi therapy. The asterisk (*) indicates a significant difference from baseline ($p < .01$).

$p = .002$) (Figure 3). CRT and BCVA measurements were available for 89.9% and 93.1% of all follow-up visits, respectively. Imputing missing data by the LOCF method did not change the outcome (data not shown).

The proportion of patients on systemic corticosteroids (Figure 1) decreased from 88.5% at baseline to 15.4% at 4 years of follow-up. The mean daily prednisone equivalent dosage could be reduced from 15.1 mg/day to 1.1 mg/day

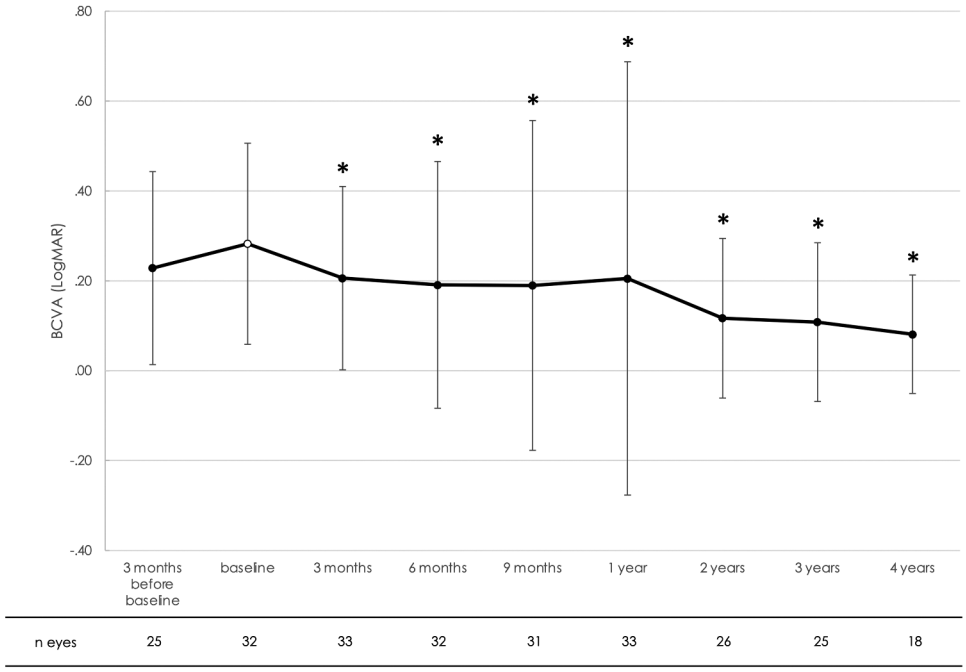

Figure 3. Evolution of best corrected visual acuity (BCVA; logMar) in patients on TNFi therapy. The asterisk (*) indicates a significant difference from baseline ($p < .01$).

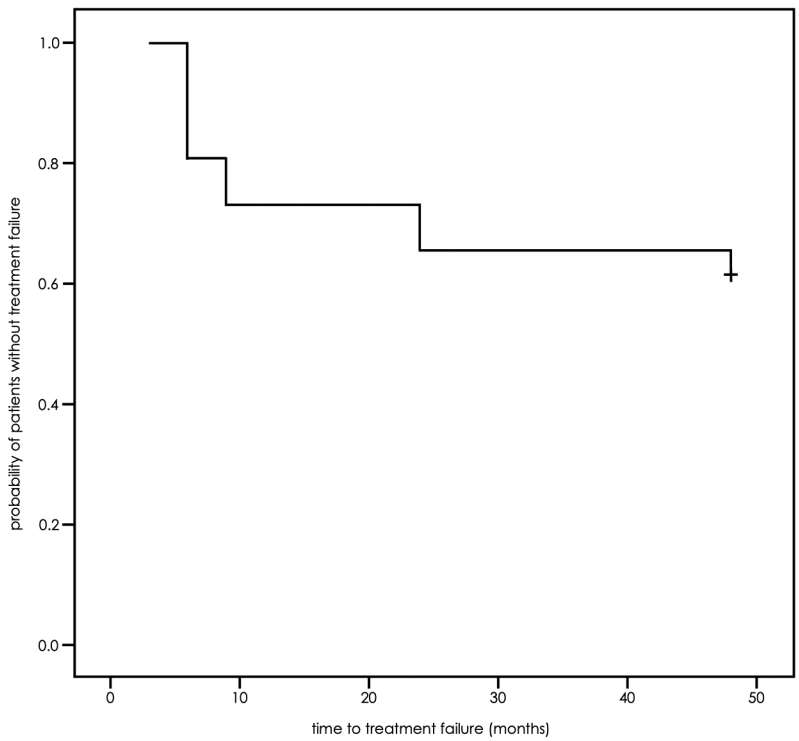

Figure 4. Time to treatment failure. The Kaplan–Meier curve depicts the probability of TNFi-treatment failure over time.

during this period of time (baseline 15.1 mg/day, 3 months 12.0 mg/day, 6 months 7.0 mg/day, 9 months 2.6 mg/day, 1 year 2.1 mg/day, 2 years 2.4 mg/day, 3 years 1.1 mg/day and 4 years 1.1 mg/day). On the other hand, the percentage of patients on a csDMARD increased between baseline and the end of follow-up from 53.8% at baseline to 76.9% at 4 years of follow-up. No patient was switched to another biologic agent (besides a TNFi) during the observation period (only switches from ADA to IFX or vice versa were reported). A total of 10 patients (38.5%) met the definition of TNFi treatment failure, with a mean time to treatment failure of 14.4 ± 13.8 months (median 7.5 month, IQR: 6 to 20.3 months) (Figure 4). Of these, three patients (five eyes) required intercurrent systemic corticosteroid pulses, three patients (three eyes) had an intravitreal corticosteroid injection, and four patients (four eyes) had a corticosteroid implant (Figure 5).

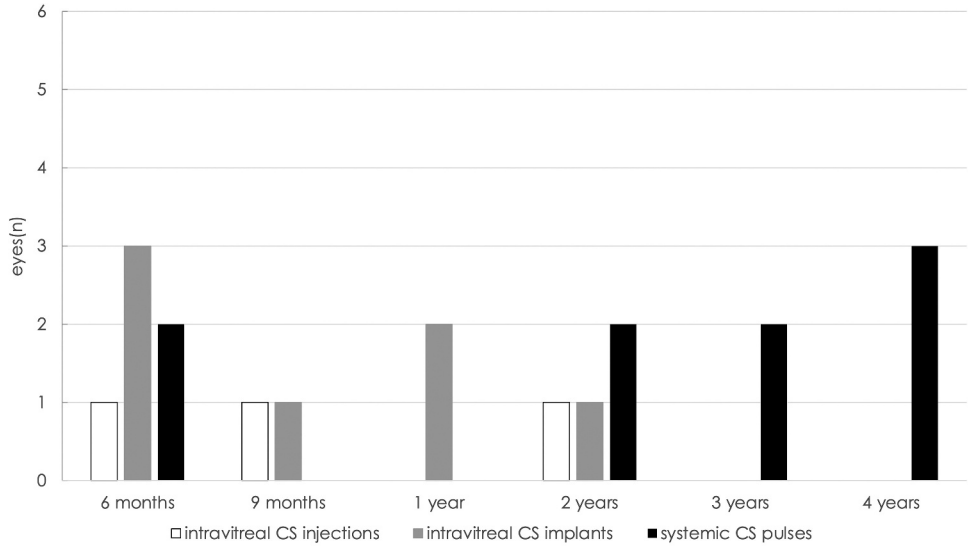

Figure 5. Rescue therapy with corticosteroids (CS) beyond 3 months after TNFi treatment was necessary in a total of 12 eyes (34.3%) in 10 patients (38.5%). Number of eyes requiring CS rescue interventions is shown for each follow-up period.

Discussion

Our series demonstrates a beneficial effect of TNFi therapy on longstanding uveitic ME insufficiently responsive to corticosteroids and csDMARDs, with relevant improvement of anatomic and functional parameters, as well as a reduced corticosteroid demand in the majority of patients over 4 years. Indeed, a complete resolution of ME (CRT < 300 µm and/or reduction of CRT > 30%) was achieved in 69.2% of our patients (72.2% of eyes). BCVA remarkably improved in parallel until the end of follow-up in our cohort. These outcomes compare well to the 1- and 2-year BCVA outcomes reported recently[23] and add evidence for the long-term success of TNFi treatment. Our results are supported by a study of Lejoyeux et al. in 25 patients with uveitic ME as well as a recent publication of Kunimi and colleagues in patients with uveitis associated with Behçet's disease and sarcoidosis.[24,25] Kunimi et al. found IFX and ADA to be equally effective in controlling uveitis, while ADA was superior in the control of uveitic ME in patients with Behçet's disease compared to sarcoidosis.

ME is a common complication of endogenous uveitis and has a relevant impact on the quality of life of patients, as it affects not only visual acuity and contrast sensitivity but also namely near visual tasks and thereby professional activities.[26,27] Chronic ME bears a relevant risk for persistent structural damage to the fovea with neuroretinal atrophy and irreversible vision loss.[6] This explains why a decrease of CRT in longstanding ME is not always associated with an improvement in visual function.[28–31]

Inflammatory ME results from a breakdown of the inner and outer blood-retinal barriers, which is orchestrated by a variety of cytokines and inflammatory cells (i.e., macrophages and neutrophils). The activity of these cells and cytokines may be controlled by nonspecific therapy (corticosteroids and/or csDMARDs) or specifically with biological treatments, such as TNFi therapy.[27] Two prospective randomized trials have led to the approval of ADA for the treatment of noninfectious intermediate, posterior and panuveitis.[10,11] Additionally, a Delphi-based treatment recommendation has summarized the evidence for csDMARD and bDMARD treatments in noninfectious uveitis.[32] However, the effect of TNFi therapy on chronic uveitic ME as an important vision-threatening complication of uveitis has not systematically been addressed up to now, especially not regarding their long-term efficacy. Systemic corticosteroids and intravitreal injections or implants have been used as first- and second-line treatments for uveitic ME. Furthermore, intravitreal injections of anti-VEGF and systemic and local carbonic anhydrase inhibitors may have a limited additional benefit in these patients.[33–37] Based on published evidence and supported by our long-term outcomes, treatment should be supplemented early with a TNFi if uveitis or uveitic ME is not completely controlled by first- and second-line treatment options or if these are not tolerated by patients. Considering the 38.5% failure rate in our study, other biologicals such as tocilizumab might be considered if uveitic ME is refractory to TNFi treatment to prevent permanent structural damage to the fovea.[38,39] The use of interferon as an immunomodulating therapy is another option for achieving remission in uveitis and uveitic ME.[40] Promising data about interferon beta on uveitic ME have been published by Mackensen et al. in a prospective study comparing the efficacy of interferon beta to MTX.[41] The drug is available for the treatment of multiple sclerosis in Switzerland, it's use in uveitis would be off label. On the other hand, interferon alpha showed efficacy on uveitic ME in patients with Behçet's disease.[42] However, the drug has recently been taken of the Swiss market.

A relevant steroid-sparing effect was achieved in our patients, which has also been reported in the VISUAL-3 trial.[43,44] This confirms, in a real-life setting, the findings of the VISUAL-1 and −2 trials, which demonstrated that ADA is efficient at controlling uveitis activity and allows to taper systemic corticosteroids in 81% of patients after 24 months compared to baseline.[10,11] Similar findings have also been reported for IFX.[45] Adding thereto, our data demonstrate that the corticosteroid-sparing potential is maintained for at least 4 years in real-life. However, 10 patients (38.5%) in our series needed corticosteroid rescue treatment after initiation of TNFi therapy, with five of them needing repeated rescue interventions (2 and ≥3 rescue interventions in two and three patients, respectively). Indeed, TNFi therapy is effective over the long-term

in a real-life setting but may require an additional short-term intervention with corticosteroid injections/implants during the course of disease in case of a flare-up of inflammation. In terms of the long-term side effects of corticosteroids, this still represents a relevant improvement. No relevant decrease of csDMARD treatment was observed after starting TNFi therapy. This may, at least partially, be explained by the common use of csDMARDs, especially methotrexate, as an accompanying treatment to TNFi agents to prevent the development of anti-drug antibodies and to improve TNFi efficacy as reported previously.[46]

Our data emphasize the need for a long-term therapeutic strategy and regular re-evaluation of these chronically ill patients to balance treatment expectations to the outcomes regarding uveitis activity and ME. Interestingly, only 10 (38.5%) of our patients with uveitis treated with a TNFi were maintained on the same TNFi over several years under real-life conditions, whether it be due to remission (n = 6), flares of uveitis or associated disease activity despite treatment (n = 6), side effects (n = 2), remission but another flare-up after discontinuation (n = 1) or for unknown reasons (n = 1). Nevertheless, TNFi therapy generally appears to control ME and improve visual function over the long-term in clinical practice.

Symptomatic demyelinating lesions under TNFi are rare and typically observed during the first year of treatment.[47,48] Since none of our patients reported indicative neurological symptoms, no systematic or repeated neuroimaging was performed during TNFi treatment.

Most published studies reporting the effects of TNFi therapy had follow-up times of maximally 2 years and focused on uveitis activity and flares but not on uveitic ME.[49–51] Our multicenter approach, including all tertiary care uveitis centers in Switzerland, allowed to provide long-term outcomes in a relatively large cohort of patients with uveitis who had persistent ME while being treated with csDMARDs requiring TNFi therapy. Inherent limitations of our study are linked to its retrospective nature, including an incomplete data set, certain variations in follow-up times and different treatment strategies in the single centers, namely the use and timing of csDMARDs and/or rescue treatments. As all participating clinics are tertiary uveitis referral centers, a selection bias for more severe cases of uveitic ME has to be assumed. This study does not allow any conclusion about the risk for relapses of uveitis or ME after stopping the TNFi, as the follow-up was censored at the time-point of TNFi discontinuation.

The mean uveitis duration of 2.9 years before initiation of TNFi therapy in our patients is typical for uveitis patients. The outcome in our cohort might have been even more favorable if TNFi treatment would have been established earlier as has been established in recent years. Indeed, the approval of ADA has allowed its use in chronic intermediate, posterior or panuveitis, even directly after an initial corticosteroid course in cases of insufficient response and/or high need for systemic corticosteroids.[10,11,44] However, in daily routine, csDMARDs are still quite commonly used as a cost-saving second-line treatment before a TNFi is initiated, which was also the rule in our patients.

In summary, the addition of TNFi led to improvement of both CRT and BCVA during up to 4 years of follow-up, although intercurrent rescue treatments were needed in some patients. Anti-TNFi use also showed a corticosteroid sparing effect in our patients.

It remains to be shown if earlier initiation of TNFi therapy would have resulted in even more favorable morphological and anatomic outcomes.

Disclosure statement

Justus G. Garweg acts as an advisor for several pharmaceutical companies (AbbVie, Alcon, Roche, Bayer and Novartis) and participates in several international industry-sponsored clinical studies without any bearing on this work. All authors declare that they have no potential conflict of interests.

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