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Anti–Tumor Necrosis Factor α versus Tocilizumab in the Treatment of Refractory Uveitic Macular Edema

A Multicenter Study from the French Uveitis Network

Mathilde Leclercq, MD,[1,2,] Anaïs Andrillon, MD,[3,*] Georgina Maalouf, MD,[2,*] Pascal Sève, MD, PhD,[4] Philip Bielefeld, MD, PhD,[5] Julie Gueudry, MD, PhD,[6] Thomas Sené, MD,[7] Thomas Moulinet, MD,[8] Bénédicte Rouvière, MD,[9] Damien Sene, MD, PhD,[10] Anne-Claire Desbois, MD, PhD,[2] Fanny Domont, MD,[2] Sara Touhami, MD, PhD,[11] Carolla El Chamieh, MD,[3] Patrice Cacoub, MD, PhD,[2] Bahram Bodaghi, MD, PhD,[11] Lucie Biard, MD, PhD,[3] David Saadoun, MD, PhD[2]*

Purpose: To analyze the factors associated with response (control of ocular inflammation and corticosteroid-sparing effect) to biologics (anti–tumor necrosis factor [TNF]-α agents and tocilizumab) in patients with refractory uveitic macular edema (ME).

Design: Multicenter, retrospective, observational study.

Participants: Adult patients with uveitic ME refractory to systemic corticosteroids, disease-modifying anti-rheumatic drugs, or both.

Methods: Patients received anti–TNF-α agents (infliximab 5 mg/kg at week 0, 2, 6, and every 4–6 weeks [n = 69] and adalimumab 40 mg/2 weeks [n = 80]) and tocilizumab (8 mg/kg every 4 weeks intravenously [n = 39] and 162 mg/week subcutaneously [n = 16]).

Main Outcome Measures: Analysis of complete and partial response rates, relapse rate, low vision (visual acuity in at least 1 eye of ≥ 1 logarithm of the minimum angle of resolution), corticosteroid-sparing effect, and adverse events at 6 months.

Results: Two hundred four patients (median age, 40 years [interquartile range, 28–58 years]; 42.2% men) were included. Main causes of uveitis included Behçet's disease (17.2%), birdshot chorioretinopathy (11.3%), and sarcoidosis (7.4%). The overall response rate at 6 months was 46.2% (21.8% of complete response) with anti–TNF-α agents and 58.5% (35.8% of complete response) with tocilizumab. In multivariate analysis, treatment with tocilizumab (odds ratio, 2.10; 95% confidence interval [CI], 1.06–4.06; $P = 0.03$) was associated independently with complete response of uveitic ME compared with anti–TNF-α agents. Anti–TNF-α agents and tocilizumab did not differ significantly in terms of relapse rate (hazard ratio, 1.00; 95% CI, 0.31–3.18; $P = 0.99$) or occurrence of low vision (odds ratio, 1.02; 95% CI, 0.51–2.07; $P = 0.95$) or corticosteroid-sparing effect ($P = 0.29$). Adverse events were reported in 20.6% of patients, including serious adverse events reported in 10.8% of patients.

Conclusions: Tocilizumab seems to improve complete response of uveitic ME compared with anti–TNF-α agents. *Ophthalmology 2022;129:520-529 © 2021 by the American Academy of Ophthalmology*

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Noninfectious inflammatory uveitis is a heterogeneous group of diseases characterized by inflammation of intraocular structure. It can be associated with systemic autoimmune diseases or can be sporadic and of unknown cause. With a prevalence of 121 per 100 000 persons,[1] uveitis is 1 of the 5 common causes of visual loss in industrialized countries.[2] Cataract, glaucoma, and macular alterations account for the main ocular complications of uveitis.[3,4]

Uveitic macular edema (ME) is related to the breakdown of the outer or the inner blood–retinal barrier, or both, secondary to chronic inflammation and secretion of proinflammatory factors such as tumor necrosis factor (TNF)-α, prostaglandins, and vascular endothelial growth factor.[5,6] These proinflammatory factors result in an increase of permeability of the retinal pigment epithelium and the retinal vasculature.[7,8] Uveitic ME is more common in patients with intermediate uveitis (25%–70%), posterior

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uveitis (19%−34%), and panuveitis (18%−66%). Uveitic ME is responsible for a severe decrease of visual acuity (VA) in one-third of patients with posterior uveitis,[9] supporting an effective therapeutic management.

Several treatments can be used for uveitic ME management. Local corticosteroids, with periocular injections or, mostly, intravitreal implants of corticosteroids, usually are proposed in cases of unilateral uveitic ME, in the absence of associated systemic disease, or as an adjunct to systemic therapy.[7] Intravitreal implants of dexamethasone (Ozurdex) have been shown to improve VA by more than 2 lines in 50% of patients. However, in a recent literature review, almost one-third of patients did not show any visual improvement despite a decrease of central foveal thickness (CFT).[10] Fluocinolone acetonide implant (Retisert) also has shown efficacy in uveitis treatment. Recently, Tomkins-Netzer et al[11] reported that the cumulative percent of eyes with resolution of cystoid ME was 94% within the 7 years of follow-up, with a median time to resolution of 1 year. However, the cumulative percentage of eyes showing relapse of uveitic ME was 43%. Conventional immunosuppressive drugs such as mycophenolate mofetil, methotrexate, or azathioprine have shown their efficacy in the resolution of uveitic ME.[12,13] Interestingly, systemic immunosuppressive drugs have shown their efficacy on uveitic ME resolution with fewer adverse events than corticosteroid implant.[14] Biotherapies seem to be an attractive option in the treatment of uveitic ME, although few data are available. Adalimumab, an anti−TNF-α antibody, has been approved by the US Food and Drug Administration and the European Medicine Agency for the treatment of patients with noninfectious nonanterior uveitis in case of corticosteroid dependency[15] or contraindication to corticosteroids.[16] However, it is a priority to evaluate ME as a trial end point because it is a major cause of functional visual loss in uveitis. A Cochrane review[17] reported that no prospective study has focused on the resolution of uveitic ME with biologics. The efficacy of anti−TNF-α agents and tocilizumab, an anti−interleukin-6 receptor, in the resolution of ME has been suggested in a few retrospective studies.[18−20]

Data regarding factors associated with response to anti−TNF-α agents or tocilizumab are lacking in refractory ME in noninfectious uveitis. In the Biotherapies in Macular Edema and Retinal Vasculitis (BIOVAS) study from the French Uveitis Network, our aim was to analyze the efficacy, as well as adverse events, of anti−TNF-α agents and tocilizumab to control ocular inflammation and corticosteroid-sparing effect in a large retrospective cohort of patients with refractory ME in the context of noninfectious uveitis.

Methods

Patients

This was a multicenter, retrospective, observational study conducted in participating internal medicine and ophthalmology departments of the French Uveitis Network between 2018 and 2020. Adult patients with refractory uveitic ME were included. Refractory ME was defined as ME resistant to a first-line therapy with systemic corticosteroids or disease-modifying antirheumatic drugs (i.e., mycophenolate mofetil, methotrexate, azathioprine, etc.) and that requires treatment escalation with anti−TNF-α agents (adalimumab or infliximab) or tocilizumab. Uveitic ME was defined by a CFT of more than 300 μm measured with spectral-domain OCT and the presence of intraretinal cystic spaces or subretinal fluid in the absence of choroidal neovascularization. Patients were excluded if they demonstrated noninfectious uveitis without ME or ME unrelated to uveitis. Patients previously treated with intravitreal implants of dexamethasone within 6 months were excluded.

The study complied with the ethical principles of the Declaration of Helsinki. This study was approved by the local ethics committee of Pitié-Salpêtrière Hospital (identifier, 1867484). Informed consent was not required as per French regulations for research on humans because of the retrospective, strictly observational nature of the study.

Study Treatment

Infliximab (IFX) was administered intravenously at 5 mg/kg at week 0, 2, and 6, and every 4 to 6 weeks thereafter, left to the discretion of the clinician. Adalimumab was administered subcutaneously at 80 mg then 40 mg every 2 weeks. Tocilizumab was administered at 8 mg/kg every 4 weeks intravenously or at a dose of 162 mg every week subcutaneously. The choice of biotherapy was left to the discretion of the clinician.

Data Collection

Collected data included demographic characteristics (age, sex, date of diagnosis), treatment characteristics (concomitant treatment, corticosteroid dose, adverse events), uveitis characteristics (cause, anatomic localization according to the Standardization of Uveitis Nomenclature criteria[21]), course of VA (Snellen and logarithm of the minimum angle of resolution [logMAR]), evolution of anterior chamber cells according to Standardization of Uveitis Nomenclature classification,[21] evolution of vitreous haze grade according to the classification of Nussenblatt et al,[22] and presence of vasculitis based on fluorescein angiography. Central foveal thickness was measured with OCT (Cirrus HD-OCT [Carl Zeiss Meditec] and Spectralis [Heidelberg Instruments]). For bilateral uveitic ME, the most affected eye was considered for analysis.

Study End Points

The primary objective was the complete response of uveitic ME at 6 months. Complete response was defined as a complete resolution of uveitic ME (CFT, $\leq$ 300 μm with resolution of intraretinal cystic spaces) and a corticosteroid dosage of 10 mg/day or less at 6 months, without intraocular inflammation (grade 0 for anterior chamber cells and vitreous haze[22]). Partial response was defined as an improvement of ME without complete resolution, an improvement of intraocular inflammation, and a reduction of the initial corticosteroid dosage at 6 months. Patients showing complete resolution of uveitic ME with a corticosteroid dosage of more than 10 mg/day at 6 months also were considered to be partial responders. The remaining patients were considered to be nonresponders.

Secondary end points included factors associated with relapse of uveitic ME, factors associated with low VA, and adverse events. Relapse was defined as an increase of macular thickness requiring a change in therapeutic strategy (increase of corticosteroid dose, intraocular corticosteroid injection, or another biotherapy) in at

least 1 eye. Low vision was defined as VA in at least 1 eye of 20/200 or worse (1 logMAR).

For the evaluation of primary and secondary end points, each treatment line was considered per patient for univariate and multivariate analysis. A line of treatment was defined as the sequence from the initiation of a new therapeutic strategy to the next one or last follow-up. We assumed treatment lines were independent.

Statistical Analysis

Data on categorical variables were summarized as number and percentage and were compared using the Fisher exact test. Data on continuous variables were summarized as the median and interquartile range (IQR) and were compared using the Wilcoxon test or Kruskal-Wallis test. For the evaluation of primary and secondary end points, each treatment line was considered per patient for univariate and multivariate analysis. Factors associated with complete response or low vision were assessed using logistic regression. Factors associated with relapse were assessed using Cox proportional hazards models. For both end points, an adjusted multivariate model was used with backward variable selection based on Akaike's information criterion. Clinically relevant variables were candidates for the stepwise selection, and the treatment group variable was forced into the adjusted model. Cumulative incidences of relapse were estimated using the Kaplan-Meier

Table 1. Demographic and Clinical Characteristics of the 204 Patients with Refractory Uveitic Macular Edema

Parameter	Total (n = 204)	Anti–Tumor Necrosis Factor-α (n = 149)	Tocilizumab (n = 55)	*P* Value
Age (yrs)	40 (28–58)	39 (25–57)	47 (32–64)	0.03
Male sex	86 (42.2)	66 (44.3)	20 (36.4)	0.43
Geographic ancestry				0.49
Europe	148 (72.5)	104 (69.8)	44 (80)	
North Africa	25 (12.3)	21 (14.1)	4 (7.3)	
Sub-Saharan Africa	19 (9.3)	15 (10.1)	4 (7.3)	
Asia	7 (3.4)	5 (3.4)	2 (3.6)	
NA	5	4	1	
Uveitis cause				0.03
Idiopathic	97 (47.5)	63 (42.3)	34 (61.8)	
Behçet's disease	35 (17.2)	32 (21.5)	3 (5.5)	
Birdshot chorioretinopathy	23 (11.3)	17 (11.4)	6 (10.9)	
Sarcoidosis	15 (7.4)	14 (9.4)	1 (1.8)	
Juvenile idiopathic arthritis	12 (5.9)	10 (6.7)	2 (3.6)	
Vogt-Koyanagi-Harada disease	8 (3.9)	6 (4)	2 (3.6)	
Spondyloarthritis	5 (2.4)	4 (2.7)	1 (1.8)	
Other	9 (4.4)	5 (3.4)	4 (7.3)	
Uveitis characteristics				
Bilateral	172 (84.3)	127 (85.2)	45 (81.8)	0.70
Chronic	173 (84.8)	134 (89.9)	39 (70.9)	0.45
Granulomatous	39 (19.1)	27 (18.1)	12 (21.8)	0.54
Vitreous haze grade (Nussenblatt et al classification, ≥ 1)	100 (49)	69 (46.3)	31 (56.4)	0.18
Retinal vasculitis	77 (37.7)	60 (40.3)	17 (30.9)	0.27
Localization				0.54
Anterior uveitis	10 (4.9)	8 (5.4)	2 (3.6)	
Intermediate uveitis	25 (12.3)	17 (11.4)	8 (14.5)	
Posterior uveitis	65 (31.9)	46 (30.9)	19 (34.5)	
Panuveitis	110 (53.9)	84 (56.4)	26 (47.3)	
Snellen visual acuity, right eye	20/50	20/50	20/63	
Median visual acuity, right eye (logMAR)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.5 (0.2–1.0)	0.39
Snellen visual acuity, left eye	20/50	20/50	20/50	
Median visual acuity, left eye (logMAR)	0.4 (0.2–0.7)	0.4 (0.1–0.7)	0.4 (0.2–0.7)	0.89
Visual acuity ≥ 1 logMAR	58 (31.7)	42 (28.2)	16 (29.1)	0.69
Adalimumab		18 (42.9)		
Infliximab		24 (57.1)		
Central foveal thickness (μm)	350 (300–498)	344 (288–491)	356 (304–527)	0.22
Concomitant treatment with corticosteroid	183 (89.7)	134 (89.9)	49 (89.1)	0.86
Initial corticosteroid dose (mg/d)	20 (10–30)	20 (10–30)	15 (8–20)	0.78
Concomitant treatment with immunosuppressive drugs	82 (40.2)	58 (38.9)	22 (40)	0.51
Methotrexate	26 (37.1)	18 (31)	6 (27.3)	
Mycophenolate mofetil	5 (6.1)	3 (5.2)	2 (9.1)	
Azathioprine	11 (13.4)	9 (15.5)	2 (9.1)	
Others	40 (48.8)	28 (48.3)	12 (54.5)	

logMAR = logarithm of the minimum angle of resolution. NA = not available.
Data are presented as median (interquartile range) or number (percentage).

Table 2. Univariate Analysis of Factors with Complete Response, Relapse, and Low Visual Acuity

Parameter	Complete Response		Relapse		Low Vision	
	Odds Ratio (95% CI)	P *Value*	*Hazard Ratio (95% CI)*	P *Value*	*Odds Ratio (95% CI)*	P *Value*
Male sex	0.87 (0.49−1.52)	0.62	1.17 (0.75−1.84)	0.49	0.91 (0.52−1.58)	0.74
Age (yrs)	0.99 (0.98−1.01)	0.47	1.01 (1.00−1.02)	0.22	0.99 (0.98−1.01)	0.21
Cause		0.16		**0.012**		
Idiopathic uveitis	1		**1**		**1**	**0.021**
Behçet's disease	0.73 (0.29−1.84)		**0.42 (0.22−0.81)**		2.96 (1.38−6.38)	
Others	1.54 (0.86−2.78)		**0.59 (0.36−0.96)**		1.46 (0.80−2.65)	
Concomitant immunosuppressive drugs	1.16 (0.67−2.03)	0.60	0.82 (0.52−1.31)	0.41	1.39 (0.80−2.40)	0.24
Initial corticosteroid dose (mg/d)	0.64 (0.29−1.46)	0.29	1.01 (0.5−2.02)	0.98	0.49 (0.22−1.09)	0.08
Bilateral uveitis	0.59 (0.29−1.18)	0.14	1.03 (0.55−1.91)	0.93	1.08 (0.53−2.22)	0.83
Anterior uveitis	1.38 (0.41−4.63)	0.61	0.69 (0.17−2.81)	0.60	1.80 (0.53−6.09)	0.34
Intermediate uveitis	1.87 (0.87−4.04)	0.11	0.79 (0.34−1.84)	0.59	0.54 (0.21−1.38)	0.20
Posterior uveitis	0.69 (0.37−1.28)	0.23	**1.56 (0.98−2.49)**	**0.062**	1.18 (0.67−2.09)	0.57
Panuveitis	0.91 (0.52−1.57)	0.73	0.84 (0.53−1.32)	0.45	0.93 (0.54−1.58)	0.78
Treatment		**0.027**		0.99		0.95
Anti−TNF-α agents	**1**		1		1	
Tocilizumab	**2.08 (1.09−3.99)**		1.00 (0.31−3.18)		1.02 (0.51−2.07)	
Patients treated with anti−TNF-α agents		0.87		**0.0007**		**0.024**
Adalimumab	1		**1**		**1**	
Infliximab	0.95 (0.50−1.79)		**0.43 (0.27−0.70)**		**2.01 (1.10−3.67)**	
Patients treated with tocilizumab		0.15		0.38		0.86
Intravenous	1		1		1	
Subcutaneous	0.38 (0.10−1.42)		3.46 (0.22−55.8)		0.89 (0.23−3.42)	

CI = confidence interval; TNF = tumor necrosis factor. Boldface indicates statistical significance.

method. Statistical analyses were performed using R Studio version 3.6.1, and *P* values of less than 0.05 were considered to be statistically significant.

Results

Baseline data are summarized in Table 1. Two hundred four patients (57.8% women; median age, 40 years [IQR, 28−58 years]) were included in the study: 149 patients (73%) were treated with anti−TNF-α agents (80 with adalimumab and 69 with infliximab) and 55 patients (27%) received tocilizumab (39 intravenous and 16 subcutaneous). One hundred ten patients (53.9%) had panuveitis and 77 patients (37%) had retinal vasculitis. The main causes of uveitis were Behçet's disease (35 patients [17.2%]), birdshot chorioretinopathy (23 patients [11.3%]), and sarcoidosis (15 patients [7.4%]). One hundred eighty-three patients (89.7%) and 82 patients (40.2%) received systemic corticosteroids or disease-modifying antirheumatic drugs, respectively, in combination with anti−TNF-α agents or tocilizumab. Patients treated with tocilizumab were significantly older ($P = 0.03$) and uveitis causes were significantly different between the 2 groups ($P = 0.03$). Forty-two patients (76%) treated with tocilizumab previously had received anti−TNF-α agents. Most of patients had been treated previously with disease-modifying antirheumatic drugs: 82% in the anti−TNF-α group and 87% in the tocilizumab group ($P = 0.40$). Median time to follow-up was 74.5 months (IQR, 37−137 months), with a median time of 88 months (IQR, 37−144 months), 72.5 months (IQR, 39−131 months), and 76 months (IQR, 38−135 months) for infliximab, adalimumab, and tocilizumab, respectively. Median time from diagnosis of uveitis to introduction of biotherapy was 40 months (IQR, 11.7−89.6 months) for anti−TNF-α agents and 29 months (IQR, 9−60 months) for tocilizumab ($P = 0.15$).

Response of Uveitic Macular Edema to Treatment

A total of 280 lines of treatment were studied, including 225 lines of anti−TNF-α agents (117 adalimumab and 108 infliximab) and 55 lines of tocilizumab. Complete response at 6 months was achieved in 24.5% patients, of whom 21.8% received anti−TNF-α agents and 35.8% received tocilizumab. Adalimumab and infliximab showed similar complete response rates: 22.2% and 21.3%, respectively.

In univariate analysis (Table 2), the factor associated with complete response was tocilizumab treatment (odds ratio, 2.08; 95% confidence interval [CI], 1.09−3.99; $P = 0.027$). In multivariate analysis, treatment with tocilizumab (odds ratio, 2.10; 95% CI, 1.06−4.06; $P = 0.03$) was associated independently with complete response of uveitic ME compared with anti−TNF-α agents (Fig 1). Partial response was obtained in 24.1% of patients, 24.4% of whom with anti−TNF-α and 22.6% of whom with tocilizumab.

Relapse of Uveitic Macular Edema

Relapse under treatment occurred in 44.6% of patients, with a median time to relapse of 41 months (IQR, 10 months−third quartile not reached) after the introduction of biological agents (Fig S2, available at www.aaojournal.org). The estimated relapse rate at 6 months after the introduction of biological agents was 16% (95% CI, 0.10−0.22). The median duration of disease control was 12 months (IQR, 6.8−28.5 months) for anti−TNF-α agents and 11 months (IQR, 6−15.3 months) for tocilizumab ($P = 0.34$).

In univariate analysis (Table 2), the factors associated with relapse risk were posterior uveitis, Behçet's uveitis, nonidiopathic uveitis, and treatment. In multivariate analysis, posterior uveitis was associated with an increased relapse

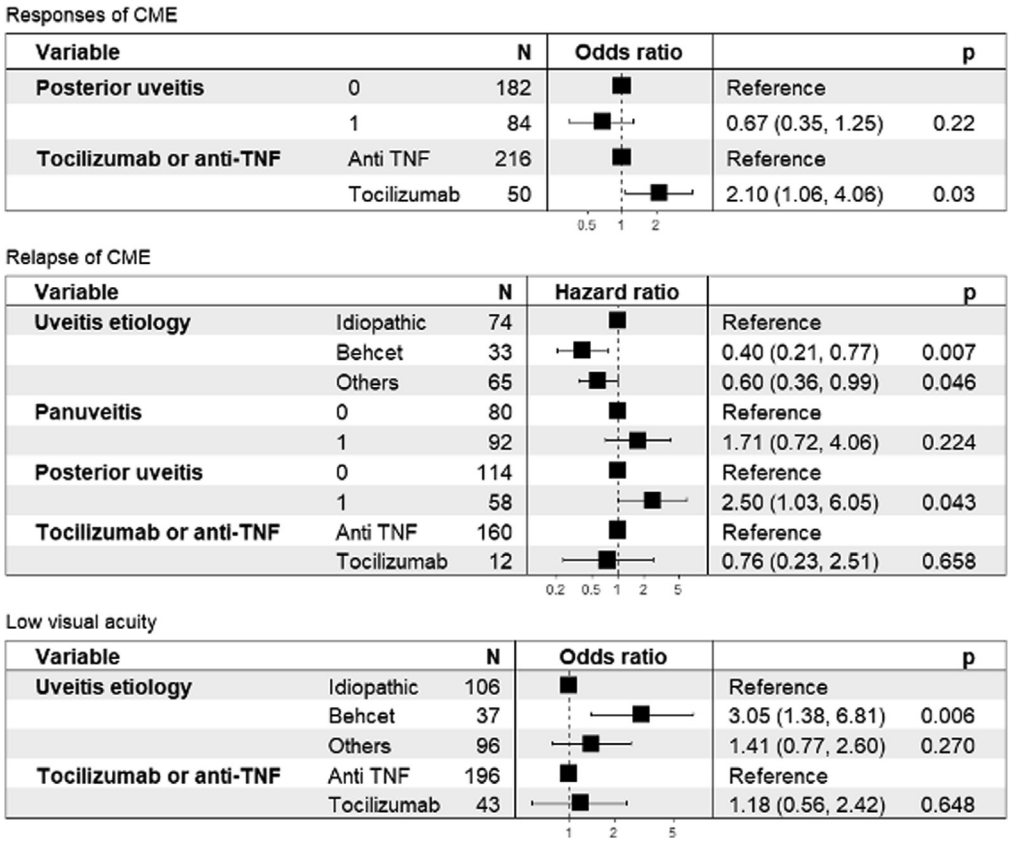

Figure 1. Forest plots showing multivariate analysis of factors associated with complete uveitic macular edema (ME) response, relapse of uveitic ME, and low visual acuity. Adjusted estimates and confidence intervals estimated by the multivariate models are provided. CME = cystoid macular edema; TNF = tumor necrosis factor.

risk (hazard ratio, 2.50; 95% CI, 1.03−6.05; $P = 0.043$), whereas Behçet's disease was associated inversely with relapse risk compared with the reference, idiopathic uveitis (hazard ratio, 0.40; 95% CI, 0.21−0.77; $P = 0.007$; Fig 1).

Low Visual Acuity

Median VA at the initiation of biological agents was 20/50 (0.4 logMAR [IQR, 0.2−0.7 logMAR]). At 6 months, VA improved to 20/40 (0.3 logMAR [IQR, 0.1−0.5 logMAR]). At 6 months, 80 patients (32.1%) showed low vision, including 66 patients (83%) treated with anti−TNF-α agents and 14 patients (17%) treated with tocilizumab.

At 6 months, in univariate analysis (Table 2), the factors associated with low VA included Behçet disease, nonidiopathic uveitis, and treatment. In multivariate analysis, Behçet's disease (odds ratio, 3.05; 95% CI, 1.38−6.81; $P = 0.006$) was associated independently with poor visual prognosis compared with the reference, idiopathic uveitis (Fig 1).

Corticosteroid-Sparing Effect

Biological agents showed a significant corticosteroid-sparing effect (Fig 3). The median daily dose of prednisone was 19 mg (IQR, 10−30 mg) at the initiation of adalimumab compared with 10 mg (IQR, 7.4−18.5 mg) after 6 months of treatment ($P < 0.0001$). For infliximab, the median daily dose decreased from 20 mg (IQR, 10−30 mg) to 10 mg at 6 months (IQR, 0−40 mg; $P = 0.0006$). For tocilizumab, the median daily dose decreased from 15 mg (IQR, 8−20 mg) to 10 mg (IQR, 0−40 mg) at 6 months ($P = 0.0006$). However, no significant difference was found for corticosteroid sparing between anti−TNF-α agents and tocilizumab ($P = 0.29$), nor between adalimumab and infliximab ($P = 0.54$) or intravenous or subcutaneous tocilizumab ($P = 0.26$).

Adverse Events

Adverse events occurred in 20.6% of patients, and serious adverse events requiring treatment discontinuation were observed in 10.8% of patients (Table 3). For anti−TNF-α agents, at least 1 adverse event occurred in 23.5% of patients, with 12.8% of serious adverse events requiring treatment discontinuation. For tocilizumab, at least 1 adverse event occurred in 12.7% of patients, with 5.5% being serious adverse events. No death occurred during follow-up. Most of adverse events were infections (54.5%), hypersensitivity reaction (18.2%), or autoimmune reaction (13.6%). Hospitalization was required for 3 infections (meningitis, *Pseudomonas aeruginosa* bacteremia, and deep abscess). No opportunistic infections occurred.

Discussion

In this multicenter study, the French Uveitis Network analyzed the efficacy of anti−TNF-α agents or tocilizumab to control ocular inflammation and corticosteroid-sparing

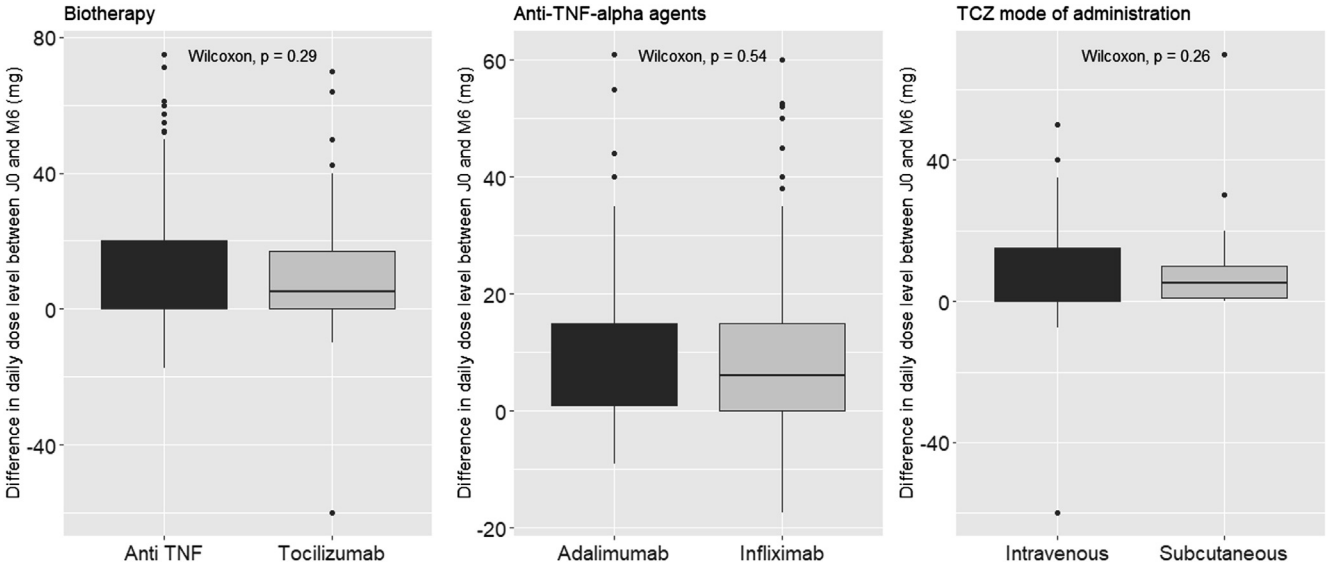

Figure 3. Box-and-whisker plots showing a comparison of corticosteroid-sparing effect between the different therapeutic strategies. TCZ = tocilizumab; TNF = tumor necrosis factor.

effect in a cohort of patients with refractory ME in sight-threatening noninfectious uveitis. The main conclusions drawn from this study are: (1) tocilizumab improved the odds of complete response of uveitic ME by 2 times as compared with anti−TNF-α agents, (2) risk of low VA in uveitic ME was increased by 3 times in Behçet's disease, and (3) adverse events observed with anti−TNF-α agents or tocilizumab were consistent with the known safety profile.

Our study showed that tocilizumab improved the odds of complete response of uveitic ME by 2 times compared with anti−TNF-α agents after 6 months of treatment. No significant difference was found between adalimumab and infliximab efficacy nor between intravenous or subcutaneous tocilizumab. The efficacy of both anti−TNF-α agents and tocilizumab[20] in uveitic ME resolution has been suggested in the literature. In the prospective VISUAL III study, Suhler et al[23] showed that patients with active uveitis (n = 242) showed an improvement in CFT after 78 weeks of treatment with adalimumab, whereas patients with inactive uveitis (n = 129) showed stability of uveitic ME. Schaap-Fogler et al[24] found a significant decrease in CFT from 515 μm to 262 μm ($P = 0.04$) after 6 months of treatment with anti−TNF-α agents. Similar results were observed with tocilizumab at 6 months (CFT decreased from 516 μm to 271 μm [$P < 0.001$])[25] or at 12 months (CFT decreased from 433 μm to 259 μm [$P < 0.0001$]).[26]

The efficacy of tocilizumab mostly has been shown for uveitic ME refractory to anti−TNF-α agents.[25,26] The originality of the BIOVAS study is that it compared anti−TNF-α agents and tocilizumab for their efficacy to resolve uveitic ME in noninfectious uveitis. Tocilizumab efficacy is supported by several experimental data from the literature. High levels of interleukin-6 were found in the aqueous humor of patients with uveitis.[27] Recently, Matas et al[28] showed a correlation between high serum levels of interleukin-6 and poor uveitic ME prognosis, whereas high levels of circulating lymphocytes T regulators were associated with uveitic ME resolution. Taken together, these results suggest that tocilizumab is a promising therapy for uveitic ME. Further prospective studies are warranted to define which biologics might be used as the first therapeutic option in sight-threatening uveitic ME. Therefore, the French Uveitis Network developed a prospective study comparing adalimumab with tocilizumab in sight-threatening uveitis (ClinicalTrials.gov identifier, NCT02929251).

Overall improvement of uveitic ME at 6 months of treatment was obtained in 46.2% with anti−TNF-α agents and 58.5% with tocilizumab. Complete and partial responses were observed in 21.8% and 24.4% of patients with anti−TNF-α agents and 35.8% and 22.6% of patients with tocilizumab, respectively. In the BIOVAS study, complete response was defined as the resolution of uveitic ME, related to the new challenge to consider sight-threating uveitis. Previous studies of adalimumab efficacy focused on the resolution of intraocular inflammation (anterior chamber, vitreous haze, or both) and found better outcomes, ranging from 70%[18,29] to 90%[30] of complete response at 6 months. These results highlight the severity of uveitic ME and the difficulty of managing these patients, despite the current development of the therapeutic arsenal. Suhler et al[23] in the VISUAL III study showed that 40% of patients with active uveitis did not respond to adalimumab therapy.

Uveitic ME has been identified as a risk factor of visual loss in uveitis. Up to 30% to 42% of patients with uveitic ME showed significant visual loss in a large study of uveitic ME.[5] Matas et al[31] highlighted bilateral uveitic ME, systemic disease, and the presence of anterior chamber cells as good prognostic factors and showed that CFT was associated unfavorably with preserved vision. In our

Table 3. Adverse Events Occurring during Biological Treatment

Adverse Event	Total	Anti−Tumor Necrosis Factor-α Agents		Tocilizumab
		Adalimumab	*Infliximab*	
Any adverse events	42 (20.6)	13 (16.3)	22 (31.9)	7 (12.7)
Serious adverse events	22 (10.8)	7 (8.8)	12 (17.4)	3 (5.5)
Death	0	0	0	0
Infection	12 (54.5)	3 (42.9)	7 (58.3)	2 (66.7)
Deep abscess	2 (16.7)	0	1 (14.3)	1 (50)
Pneumonia	1 (8.3)	0	0	1 (50)
Bacteremia (*Pseudomonas aeruginosa*)	1 (8.3)	0	1 (14.3)	0
Cutaneous infection	3 (25)	2 (66.7)	1 (14.3)	0
Herpes infections	1 (8.3)	0	1 (14.3)	0
Hepatitis (HBV)	1 (8.3)	0	1 (14.3)	0
Meningitis	1 (8.3)	0	1 (14.3)	0
Pyelonephritis	2 (16.7)	1 (33.3)	1 (14.3)	0
Nonmelanoma skin cancer	1 (4.5)	0	1 (8.3)	0
Hypersensitivity reaction	4 (18.2)	1 (14.3)	3 (25)	0
Autoimmune reactions	3 (13.6)	2 (28.6)	1 (8.3)	0
Injection-site reaction	1 (4.5)	0	0	1 (33.3)
Hallucination	1 (4.5)	1 (14.3)	0	0
Nonserious adverse events	22 (10.8)	6 (7.5)	12 (17.4)	4 (7.3)
Infections	14 (63.6)	2 (33.3)	8 (66.7)	4 (100)
Deep abscess	4 (28.6)	0	4 (50)	0
Pneumonia	2 (14.3)	1 (50)	1 (12.5)	0
Bronchitis	3 (21.4)	0	0	3 (75)
Pyelonephritis	4 (28.6)	1 (50)	2 (25)	1 (25)
Arthritis	1 (7.1)	0	1 (12.5)	0
Hypersensitivity reaction	2 (9.1)	0	2 (16.7)	0
Injection-site reaction	1 (4.5)	1 (16.7)	0	0
Headache	1 (4.5)	1 (16.7)	0	0
Isolated fever	2 (9.1)	0	2 (16.7)	0
Fatigue	2 (9.1)	2 (33.3)	0	0

HBV = hepatitis B virus.
Data are presented as no. (%).

study, we showed that the risk of low VA of uveitic ME was increased by 3 times in Behçet's uveitis. This risk has been reported in the literature and is estimated to be as high as 25% in different studies.[32,33] In a retrospective study of 107 patients with Behçet's disease, the risk of visual loss at 10 years was 39%,[34] and biologic agents were identified as protective factors. Our study highlights the poor visual prognosis of Behçet's disease despite therapeutic advances.

The adverse events observed with anti−TNF-α agents and tocilizumab in this study were consistent with the known safety profile of these biologics, and no new safety concerns were identified during longer-term exposure. No evidence of new or worsening of uveitis was observed. Serious adverse events were observed in 12.8% and 5.5% of patients with anti−TNF-α agents and tocilizumab, respectively. These results are similar to those of the VISUAL studies, where 11.7%,[15] 9.6%,[16] and 19%[23] of serious adverse events were reported. An increased risk of serious adverse events with infliximab was reported previously.[35] For tocilizumab, Vegas-Ravenga et al[26] reported 3 adverse events (nausea, viral conjunctivitis, and bullous impetigo) in 25 patients with uveitis during 12.7 months of follow-up. In the prospective STOP-Uveitis study, 2 of the 37 patients demonstrated low absolute neutrophil counts, requiring treatment discontinuation for one of them.[20]

The choice of biotherapy was up to the clinician. A potential bias in our work was a temporal bias. Indeed, anti−TNF-α agents were the first biotherapy used in the management of uveitis, before tocilizumab.[18] In the BIOVAS study, the median year of introduction of anti−TNF-α agents was 2014 (IQR, 2011−2017) compared with 2018 (IQR, 2017−2018) for tocilizumab ($P < 0.0001$). This time bias may have influenced the results in support of anti−TNF-α agents. Moreover, in our study, 76% of the patients treated with tocilizumab previously were treated with anti−TNF-α agents, but without success, suggesting more severe disease. Despite this severity and the temporal bias, tocilizumab seemed to be more effective.

The comparison of the 2 groups in our study shows a significant difference for age (older patients in the tocilizumab group) and uveitis causes. Seventy-six percent of the patients in the tocilizumab group had been treated previously with anti−TNF-α agents. Thus, it was expected that

patients in this group would be older. Concerning the etiologic diagnoses, we did not perform subgroup studies. Further studies comparing the 2 biotherapies according to uveitis causes (i.e., Behçet's disease) are ongoing. However, no significant difference was found between the 2 groups concerning initial ophthalmologic characteristics (VA, ocular inflammation, retinal vasculitis), thus allowing comparison of ophthalmic efficacy for the current episode.

We acknowledge some limitations in this study. Our analysis was performed as a retrospective review. We were unable to collect complete longitudinal data on patients who were seen only on an intermittent basis. Prospective enrollment and data collection from the time of diagnosis would have been ideal, but is more difficult to achieve with rare diseases. Although the present study compared only anti−TNF-α agents and tocilizumab based on observational nonrandomized observations, we used a logistic regression approach to minimize a potential confounding bias.

In conclusion, tocilizumab showed a tendency to be more effective than anti−TNF-α agents (infliximab or adalimumab) in the improvement of uveitic ME in this large series of refractory uveitis. In an era of biologics, Behçet's disease remains the main independent factor associated with low VA.

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[1] Internal Medicine Department, CHU Rouen, Rouen, France.

[2] Department of Internal Medicine and Clinical Immunology, Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Centre National de Références Maladies Autoimmunes et Systémiques Rares, Centre National de Références Maladies Autoinflammatoires Rares et Amylose Inflammatoire, and INSERM, UMR S 959, Immunology-Immunopathology-Immunotherapy (I3), Paris, France.

[3] Department of Biostatistics and Medical Information, CRESS UMR 1153, INSERM, ECSTRRA Team, Saint-Louis University Hospital, AP-HP, University of Paris, Paris, France.

[4] Internal Medicine Department, Hôpital de la Croix- Rousse, Hospices Civils de Lyon, and Faculté de Médecine Lyon-Sud, Université Claude Bernard-Lyon 1, Lyon, France.

[5] Internal Medicine and Systemic Diseases Department (Médecine Interne 2), Dijon University Hospital, Dijon, France.

[6] Ophthalmology Department, Hospital Charles Nicolle, CHU Rouen, and EA7510, UFR Santé, Rouen University, Rouen, France.

[7] Internal Medicine Department, Fondation Rothschild, Paris, France.

[8] Department of Internal Medicine, CHRU de Nancy, and Université de Lorraine, Inserm UMR_S 1116, Nancy, France.

[9] Internal Medicine and Pneumology Department, CHU de Brest, Hôpital La Cavale Blanche, Brest, France.

[10] Internal Medicine Department, Lariboisière Hospital, and INSERM UMR 969, University of Paris, Paris, France.

[11] Ophthalmology Department, DHU ViewRestore, Pitié Salpêtrière Hospital, Sorbonne Université, Paris, France.

*These authors contributed equally as first authors.

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Sève, Bielefeld, Sené, Cacoub, Bodaghi, Biard, Saadoun

Analysis and interpretation: Leclercq, Andrillon, Maalouf, El Chamieh, Biard, Saadoun

Data collection: Leclercq, Maalouf, Sève, Bielefeld, Gueudry, Sené, Moulinet, Rouvière, Sene, Desbois, Domont, Touhami

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Abbreviations and Acronyms:
BIOVAS = Biotherapies in Macular Edema and Retinal Vasculitis; **CFT** = central foveal thickness; **CI** = confidence interval; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **ME** = macular edema; **TNF** = tumor necrosis factor; **VA** = visual acuity.

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Correspondence:
David Saadoun, MD, PhD, Departement de Medecine Interne et d'Immunologie Clinique, Groupe Hospitalier Pitie-Salpetriere, 47-83 Boulevard de l'Hopital, 75651 Paris Cedex 13, France. E-mail: david.saadoun@aphp.fr.

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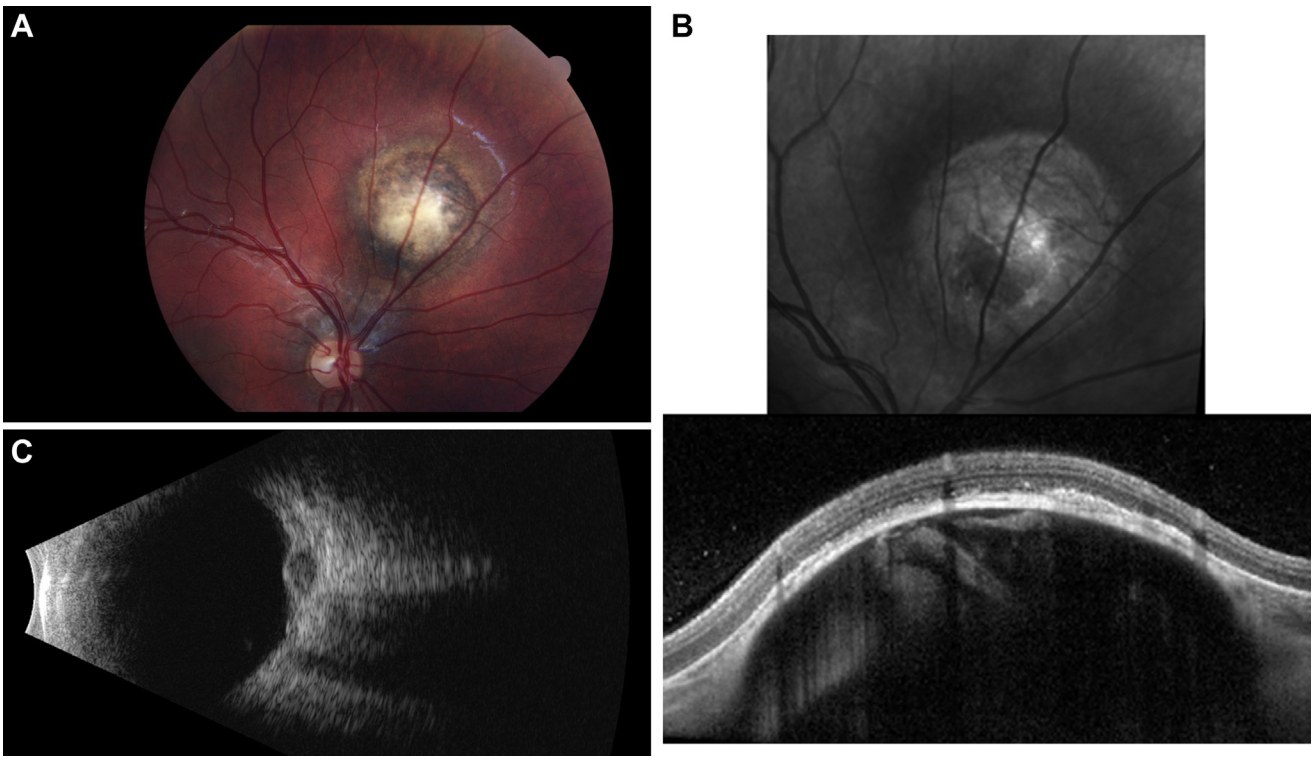
Pictures & Perspectives



Posterior Scleral Cyst in a Pediatric Patient

A 6-year-old boy presented with 20/20 vision and an incidental posterior scleral cyst of the right eye, stable in the past year. Fundus photography (Fig **A**) shows a round, circumscribed, atypical, amelanotic to minimally pigmented lesion, with discrete margins, superonasal to the optic nerve. OCT shows a scleral dome-shaped lesion superonasal to the optic nerve with a hollow appearance (Fig **B**), and trace overlying subretinal fluid (SRF), with interval increase in SRF noted inferiorly. Some material appears layered within and there is mild cell/debris overlying the lesion. B-scan ultrasonography (Fig **C**) displays a hyporeflective lesion that measures approximately 2.53 mm in height (Magnified version of Fig **A**-**C** is available online at www.aaojournal.org).

Sandra Hoyek, MD
Mary Elizabeth Aronow, MD
Nimesh A. Patel, MD

Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts