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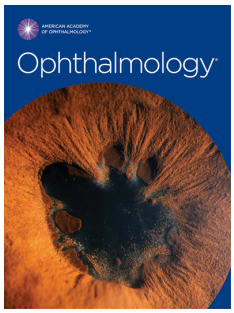

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Anti-TNF-α versus tocilizumab in the treatment of refractory uveitic macular edema: a multicenter study from the French Uveitis Network.

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Highlights:

Tocilizumab tends to be more effective than anti-TNF-α agents (infliximab or adalimumab) in this large series of refractory uveitic macular edema.

Behçet's disease is the main independent factor associated with low visual acuity.

Abstract

Objective: To analyze the factors associated with response (control of ocular inflammation and corticosteroid sparing effect) to biologics (anti-TNF-α agents and tocilizumab) in patients with refractory uveitic macular edema.

Design: Multicenter retrospective observational study.

Subjects: Adult patients with uveitic macular edema refractory to systemic corticosteroids and/or disease modifying anti-rheumatic drugs.

Methods: Patients received anti-TNF-α agents [IFX 5 mg/kg at weeks 0, 2, 6 and every 4-6 weeks (n=69) and ADA 40 mg/14 days (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 one eye ≥ 1 LogMAR), corticosteroid sparing effect and adverse events at 6 months.

Results: 204 patients (median age of 40 years [28-58] with 42.2% of men) were included. Main etiologies of uveitis included Behçet's disease (17.2%), birdshot chorioretinopathy (11.3%) and sarcoidosis (7.4%). The overall response rate at 6 months was of 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 (OR 2.10 [95% CI 1.06–4.06], p=0.03) was independently associated with complete response of uveitic macular edema, compared to anti-TNF-α agents. Anti-TNF-α agents and tocilizumab did not differ significantly in terms of relapse rate (HR=1.00 [0.31-3.18], p=0.99) or occurrence of low vision (OR=1.02 [0.51-2.07], p=0.95) or corticosteroid-sparing effect (p=0.29). Adverse events were reported in 20.6% of patients, including 10.8% of serious adverse events.

Conclusions: Tocilizumab seems to improve complete response of uveitic macular edema compared to anti-TNF-α agents.

Introduction

Non-infectious inflammatory uveitis is a heterogeneous group of diseases, characterized by inflammation of intra-ocular structure. It can be associated with systemic autoimmune diseases or be sporadic of unknown etiology. With a prevalence of 121/100,000 persons (1), uveitis is one of the five 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 (uveitic ME) is related to the breakdown of the outer and/or the inner blood-retinal barrier secondary to chronic inflammation and secretion of pro-inflammatory factors such as TNF-α (tumor necrosis factor), prostaglandins and VEGF (vascular endothelial growth factor) (5,6). These pro-inflammatory 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 uveitis (19-34%) and panuveitis (18-66%). Uveitic ME is responsible for a severe decrease of visual acuity 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, are usually proposed in cases of unilateral uveitic ME, absence of associated systemic disease or as an adjunct to systemic therapy (7). Intravitreal implants of dexamethasone (OZURDEX®) have been shown to improve visual acuity (VA) of more than 2 lines in 50% of patients. However, in a recent literature review, almost one third did not have any visual improvement despite a decrease of central foveal thickness (CFT) (10). Fluocinolone acetonide implant (RETISERT®) has also shown its efficacy in uveitis. Recently, Tomkins-Netzer et al. (11) reported that the cumulative percent of eyes with resolution of CME was 94% within the 7 years of follow-up, with a median time of resolution of one year. However, the cumulative percent of eyes with 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 appear as an attractive option in the treatment of uveitic ME, though few data are available. Adalimumab (ADA), an anti-TNF-α antibody, has been approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the treatment of patients with non-infectious non-anterior uveitis in case of corticosteroid-dependency (15) or contraindication to corticosteroids (16). However, it is a priority to evaluate macular edema as a trial endpoint because it is a major cause of functional visual loss during 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 (TCZ), an anti-IL6 receptor, in the resolution of macular edema has been suggested in few retrospective studies (18-20).

Data regarding factors associated with response to anti-TNF-α agents or TCZ are lacking in refractory ME in non-infectious uveitis. In the BIOVAS study (BIOtherapies in macular edema and retinal VAScultis) from the French uveitis network, our aim was to analyze the efficacy, as well as adverse events of anti-TNF-α agents and TCZ to control ocular inflammation and corticosteroid sparing effect in a large retrospective cohort of patients with refractory ME in non-infectious 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 macular edema resistant to a first line therapy with systemic corticosteroids and/or

disease modifying anti-rheumatic drugs (DMARDs, i.e., mycophenolate mofetil, methotrexate, azathioprine etc) and which requires treatment escalation with anti-TNF-α agents (ADA and infliximab, IFX) or TCZ. Uveitic ME was defined by a CFT of > 300 μm measured with spectral domain optical coherence tomography (OCT) and the presence of intraretinal cystic spaces or subretinal fluid in the absence of choroidal neovascularization. Patients were excluded if they presented non-infectious uveitis without macular edema or macular edema 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 (Number: 1867484). Informed consent was not required as per French regulations for research on Humans due to the retrospective strictly observational nature of the study.

Study treatment

IFX was administered intravenously at 5 mg/kg at week 0, 2, 6 and every 4-6 weeks, left at the discretion of the clinician. ADA was administered subcutaneously at 80 mg then 40 mg every 2 weeks. TCZ 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 at 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 (etiology, anatomic localization according to the Standardization of Uveitis Nomenclature [SUN] (21)), course of visual acuity (Snellen and LogMAR), evolution of anterior chamber cells according to SUN classification (21), evolution of vitreous haze grade

according to Nussenblatt classification (22), and presence of vasculitis based on fluorescein angiography). CFT was measured with OCT (Cirrus HD-OCT Carl Zeiss Meditec, Dublin, CA and Spectralis, Heidelberg Instruments, Heidelberg, Germany). For bilateral uveitic ME, the most affected eye was considered for analysis.

Study endpoints

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 ≤ 300 μm with resolution of intraretinal cystic spaces) and a corticosteroid dosage of ≤ 10 mg/ day at 6 months, without intraocular inflammation (grade 0 for anterior chamber cells and vitreous haze (22)). Partial response was defined as an improvement of macular edema without complete resolution, an improvement of intraocular inflammation and a reduction of the initial corticosteroid dosage at 6 months. Patients with complete resolution of uveitic ME with a corticosteroid dosage of > 10 mg/ day at 6 months were also considered as partial responders. The remaining patients were considered as non-responders.

Secondary end points included factors associated with relapse of uveitic ME, factors associated with low visual acuity and adverse events. Relapse was defined as an increase of macular thickness requiring a change in therapeutic strategy (increase of corticosteroid dose, intra-ocular corticosteroid injection, or another biotherapy) in at least one eye. Low vision was defined as visual acuity in at least one eye ≥ 20/200 (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 as independent.

Statistics

Data on categorical variables were summarized as number and percent and compared using Fisher's exact test. Data on continuous variables were summarized as the median and interquartile range (IQR) and were compared using Wilcoxon test or Kruskal-Wallis tests. 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 endpoints, 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 Kaplan-Meier method. Statistical analyses were performed using R Studio Version 3.6.1 and p values < 0.05 were considered to be statistically significant.

Results

Baseline data are summarized in **Table 1.** Two hundred and four patients (women [57.8%], with a median age [IQR] of 40 years old [28-58]) were included in the study: 149 patients (73%) were treated with anti-TNF-α agents (80 with ADA and 69 with IFX) and 55 patients (27%) received TCZ (39 intravenous and 16 subcutaneous). One hundred and ten (53.9%) patients had panuveitis and 77 patients (37%) had retinal vasculitis. The main etiologies of uveitis were Behçet's disease (35 patients, 17.2%), birdshot chorioretinopathy (23 patients, 11.3%) and sarcoidosis (15 patients, 7.4%). One hundred and eighty-three patients (89.7%) and 82 patients (40.2%) received systemic corticosteroids or DMARDs, respectively, in combination with anti-TNF-α agents or TCZ. Patients treated with TCZ were significantly older (p=0.03) and uveitis etiologies were significantly different between the two groups

(p=0.03). Forty-two patients (76%) treated with TCZ had previously received anti-TNF-α agents. Most of patients had been previously treated with DMARDs: 82% in the anti-TNF-α group and 87% in the TCZ group (p=0.40). Median time [IQR] to follow-up was 74.5 months [37-137], with a median time [IQR] of 88 months [37-144], 72.5 months [39-131] and 76 months [38-135] for IFX, ADA and TCZ, respectively. Median time from diagnosis of uveitis to introduction of biotherapy was 40 months [11.7-89.6] for anti-TNF-α agents and 29 months [9-60] for TCZ (p=0.15).

Response of uveitic ME to treatment.

A total of 280 lines of treatment were studied including 225 lines of anti-TNF-α agents (117 ADA/108 IFX) and 55 lines of TCZ. Complete response at 6 months was achieved in 24.5% of whom 21.8% with anti-TNF-α agents and 35.8% with TCZ. ADA and IFX had similar complete response rate: 22.2% and 21.3% respectively.

In univariate analysis **(Table 2)**, the factor associated with complete response was TCZ treatment (odds ratio OR 2.08 [95% CI 1.09–3.99], p=0.027). In multivariate analysis, treatment with TCZ (OR 2.10 [95% CI 1.06–4.06], p=0.03) was independently associated with complete response of uveitic ME, compared to anti-TNF-α agents **(Figure 1)**.

Partial response was obtained in 24.1% of whom 24.4% with anti-TNF-α and 22.6% with TCZ.

Relapse of uveitic ME.

Relapse under treatment occurred in 44.6% of patients, with a median time [IQR] to relapse of 41 months **(**Q1: 10 months, Q3 not reached) after the introduction of biological agents **(Figure 2, Supplementary data)**. The estimated relapse rate at 6 months after the introduction

of biological agents was of 16% (95% CI 0.10-0.22). The median duration of disease control was 12 months [6.8-28.5] for anti-TNF-α agents and 11 months [6-15.3] for TCZ (p=0.34).

In univariate analysis **(Table 2)**, the factors associated with relapse risk were posterior uveitis, Behçet's uveitis, non-idiopathic uveitis and treatment. In multivariate analysis, posterior uveitis was associated with an increased relapse risk (HR 2.50 [95% CI 1.03–6.05], p=0.043), whereas Behçet's disease was inversely associated with relapse risk compared to the reference (idiopathic uveitis) (HR 0.40 [95% CI 0.21–0.77], p=0.007) **(Figure 1)**.

Low visual acuity.

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

At 6 months, in univariate analysis **(Table 2)**, the factors associated with low visual acuity included Behçet disease, non-idiopathic uveitis and treatment. In multivariate analysis, Behçet's disease (OR 3.05 [95% CI 1.38–6.81], p=0.006) was independently associated with poor visual prognosis compared to the reference (idiopathic uveitis) **(Figure 1)**.

Corticosteroid sparing effect.

Biological agents had a significant corticosteroid-sparing effect **(Figure 3)**. The median [IQR] daily dose of prednisone was 19 mg [10-30] at the initiation of ADA compared to 10 mg [7.4-18.5] after 6 months of treatment (p<0.0001). For IFX, the median daily dose decreased from 20 mg [10-30] to 10 mg at 6 months [0-40] (p=0.0006). For TCZ, the median daily dose decreased from 15 mg [8-20] to 10 mg at 6 months [0-40] (p=0.0006). However, there was not

a significant difference for corticosteroid sparing between anti-TNF-α agents and TCZ (p=0.29), nor between ADA and IFX (p=0.54) and intravenous or subcutaneous TCZ (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% **(Table 3)**. For anti-TNF-α agents, at least one adverse event occurred in 23.5%, with 12.8% of serious adverse events requiring treatment discontinuation. For TCZ, at least one adverse event occurred in 12.7%, with 5.5% of serious adverse events. No death occurred during follow-up. Most of adverse events were infections (54.5%), hypersensitivity reaction (18.2%) and auto-immune reaction (13.6%). Hospitalization was required for 3 infections (meningitis, *Pseudomonas aeruginosa* bacteremia and deep abscess). There was no opportunistic infection.

Discussion

In this multicenter study, from the French uveitis network, we analyzed the efficacy of anti-TNF-α agents or TCZ to control ocular inflammation and corticosteroid sparing effect in a cohort of patients with refractory macular edema in sight-threatening non-infectious uveitis. The main conclusions drawn by this study are: 1) TCZ improved the odds of complete response of uveitic ME by 2 times as compared with anti-TNF-α agents, 2) Risk of low visual acuity of uveitic ME was increased by 3 times in Behçet's disease, 3) Adverse events observed with anti-TNF-α agents or TCZ were consistent with the known safety profile.

Our study showed that TCZ improved the odds of complete response of uveitic ME by 2 times compared with anti-TNF-α agents after 6 months of treatment. There was no significant difference between ADA and IFX efficacy nor between intravenous or subcutaneous TCZ. The

efficacy of both anti-TNF-α agents and TCZ (20) in uveitic ME resolution has been suggested in literature. In the prospective VISUAL III study, Shuler et al. showed that patients with active uveitis (n=242) had an improvement of CFT after 78 weeks of treatment with ADA whereas patients with inactive uveitis (n=129) had a stability of uveitic ME (23). Schaap-Fogler et al. found a significant decrease of 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 TCZ at 6 months (CFT decreased from 516 μm to 271 μm [p<0.001]) (24) or at 12 months (CFT decreased from 433 μm to 259 μm [p<0.0001]) (25).

The efficacy of TCZ has mostly been shown for uveitic ME refractory to anti-TNF-α agents (24,25). The originality of the BIOVAS study is to compare anti-TNF-α agents and TCZ for their efficacy to resolve uveitic ME in non-infectious uveitis. TCZ efficacy is supported by several experimental data from the literature. High levels of IL-6 were found in the aqueous humor of patients with uveitis (26). Recently, Matas et al. (27) showed a correlation between high serum levels of IL-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 TCZ 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 ADA and TCZ in sight-threatening uveitis (ClinicalTrial.gov 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 TCZ. 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% with TCZ, 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 on ADA efficacy focused on the resolution of intra-ocular inflammation (anterior chamber and/or

vitreous haze) and found better outcomes, ranging from 70% (18),(28) to 90% (29) 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 ADA.

Uveitic ME has been identified as a risk factor of visual loss in uveitis. Up to 30 to 42% of patients with uveitic ME had significant visual loss in a large study of uveitic ME (5). Matas et al. (30) highlighted bilateral uveitic ME, systemic disease and the presence of anterior chamber cells as good prognostic factors and showed that CFT was unfavorably associated with preserved vision. In our study, we showed that the risk of low visual acuity of uveitic ME was increased by 3 times in Behçet's uveitis. This risk has been reported in the literature, and estimated to be as high as 25% in different studies (31,32). In a retrospective study of 107 Behçet’s patients, the risk of visual loss at 10 years was 39% (33) 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 TCZ 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% with anti- TNF- α agents and TCZ, 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 IFX was previously reported (34). For TCZ, Vegas-Ravenga et al. (25) reported three 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,

two of the 37 patients developed 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 TCZ (18). In the BIOVAS study, the median year of introduction of anti-TNF-α agents was 2014 [2011-2017] compared to 2018 [2017-2018] for TCZ ($p<0.0001$). 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 TCZ had previously been treated with anti-TNF-α agents, but without success, suggesting more severe disease. Despite this severity and the temporal bias, TCZ appeared to be more effective.

The comparison of our two groups shows a significant difference for age (older patients in the TCZ group) and uveitis etiologies. Seventy-six percent of the patients in the TCZ group were previously treated with anti-TNF-α agents. Thus, it was expected that patients in this group would be older. Concerning the etiological diagnoses, we did not perform subgroup studies. Further studies comparing the two biotherapies according to uveitis etiologies (i.e. Behçet's disease) are ongoing. However, there was no significant difference between the two groups, concerning initial ophthalmologic characteristics (visual acuity, 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 more difficult to achieve with rare diseases. Although the present study only compared anti-TNF-α agents and TCZ based on observational non-randomized observations, we used a logistic regression approach to minimize a potential confounding bias.

In conclusion, TCZ has shown a tendency to be more effective than anti-TNF-α agents (IFX or ADA) in the improvement of uveitic ME in this large series of refractory uveitis. In an era of biologics, Behçet's disease is still the main independent factor associated with low visual acuity.

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Figure 1: Forest plots of multivariable analysis of factors associated with complete uveitic ME (macular edema) response, relapse of uveitic ME and low visual acuity. Adjusted estimates and confidence intervals estimated by the multivariable models are provided.

Figure 2 (Supplementary data) : Cumulative incidence of relapse with biological agents.

Figure 3: Comparison of corticosteroid sparing effect between the different therapeutic strategies.

Bibliography:

1. Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, et al. Prevalence of Noninfectious Uveitis in the United States: A Claims-Based Analysis. JAMA Ophthalmol. 2016;134(11):1237- 1245.
2. Tsirouki T, Dastiridou A, Symeonidis C, Tounakaki O, Brazitikou I, Kalogeropoulos C, et al. A Focus on the Epidemiology of Uveitis. Ocul Immunol Inflamm. 2018;26(1):2- 16.
3. Dick AD, Tundia N, Sorg R, Zhao C, Chao J, Joshi A, et al. Risk of Ocular Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. Ophthalmology. 2016;123(3):655- 662.
4. Prieto-Del-Cura M, González-Guijarro JJ. Risk factors for ocular complications in adult patients with uveitis. Eur J Ophthalmol. 2020;30(6):1381- 1389.
5. Massa H, Pipis SY, Adewoyin T, Vergados A, Patra S, Panos GD. Macular edema associated with non-infectious uveitis: pathophysiology, etiology, prevalence, impact and management challenges. Clin Ophthalmol Auckl NZ. 2019;13:1761- 1777.
6. de Smet MD. Insights into the Physiopathology of Inflammatory Macular Edema. Dev Ophthalmol. 2017;58:168- 177.
7. Koronis S, Stavrakas P, Balidis M, Kozeis N, Tranos PG. Update in treatment of uveitic macular edema. Drug Des Devel Ther. 2019;13:667- 680.
8. Touhami S, Beguier F, Augustin S, Charles-Messance H, Vignaud L, Nandrot EF, et al. Chronic exposure to tumor necrosis factor alpha induces retinal pigment epithelium cell dedifferentiation. J Neuroinflammation. 2018;15(1):85.
9. Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. Eye Lond Engl. 2016;30(10):1277- 1292.
10. Massa H, Georgoudis P, Panos GD. Dexamethasone intravitreal implant (OZURDEX®) for macular edema secondary to noninfectious uveitis: a review of the literature. Ther Deliv. 2019;10(6):343- 351.
11. Tomkins-Netzer O, Lightman SL, Burke AE, Sugar EA, Lim LL, Jaffe GJ, et al. Seven-Year Outcomes of Uveitic Macular Edema: The Multicenter Uveitis Steroid Treatment Trial and Follow-up Study Results. Ophthalmology. 2021;128(5):719-728.
12. Doycheva D, Zierhut M, Blumenstock G, Stuebiger N, Deuter C. Mycophenolate mofetil in the therapy of uveitic macular edema--long-term results. Ocul Immunol Inflamm. 2012;20(3):203- 211.
13. Rathinam SR, Babu M, Thundikandy R, Kanakath A, Nardone N, Esterberg E, et al. A randomized clinical trial comparing methotrexate and mycophenolate mofetil for noninfectious uveitis. Ophthalmology. 2014;121(10):1863- 1870.
14. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group, Kempen JH, Altaweel MM, Holbrook JT, Sugar EA, Thorne JE, et al. Association Between Long-Lasting Intravitreous Fluocinolone Acetonide Implant vs Systemic Anti-inflammatory Therapy and Visual Acuity at 7 Years Among Patients With Intermediate, Posterior, or Panuveitis. JAMA. 2017;317(19):1993- 2005.
15. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, et al. Adalimumab in Patients with Active Noninfectious Uveitis. N Engl J Med. 2016;375(10):932- 943.
16. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. The Lancet. 2016;388(10050):1183- 1192.
17. Barry RJ, Tallouzi MO, Bucknall N, Mathers JM, Murray PI, Calvert MJ, et al. Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis. Cochrane Database Syst Rev. 2018;12:CD012577.

18. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, Cordero-Coma M, Ortega G, Ortego N, et al. Treatment of Refractory Uveitis with Adalimumab: A Prospective Multicenter Study of 131 Patients. Ophthalmology. 2012;119(8):1575- 1581.
19. Lejoyeux R, Diwo E, Vallet H, Saadoun D, Tezenas du Montcel S, Bodaghi B, et al. Infliximab and Adalimumab in Uveitic Macular Edema. Ocul Immunol Inflamm. 2018;26(7):991- 996.
20. Sepah YJ, Sadiq MA, Chu DS, Dacey M, Gallemore R, Dayani P, et al. Primary (Month-6) Outcomes of the STOP-Uveitis Study: Evaluating the Safety, Tolerability, and Efficacy of Tocilizumab in Patients with Non-Infectious Uveitis. Am J Ophthalmol. 2017;183:71-80.
21. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509- 516.
22. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985;92(4):467- 471.
23. Suhler EB, Adán A, Brézin AP, Fortin E, Goto H, Jaffe GJ, et al. Safety and Efficacy of Adalimumab in Patients with Noninfectious Uveitis in an Ongoing Open-Label Study: VISUAL III. Ophthalmology. 2018;125(7):1075- 1087.
24. Mesquida M, Molins B, Llorenç V, Hernández MV, Espinosa G, Sainz de la Maza M, et al. Twenty-four month follow-up of tocilizumab therapy for refractory uveitis-related macular edema. Retina Phila Pa. 2017;38(7):1361-1370.
25. Vegas-Revenga N, Calvo-Río V, Mesquida M, Adán A, Hernández MV, Beltrán E, et al. Anti-il6-r tocilizumab in refractory and non-infectious uveitic cystoid macular edema. Multicenter study of 25 patients. Am J Ophthalmol. 2019;200:85-94.
26. Weinstein JE, Pepple KL. Cytokines in uveitis. Curr Opin Ophthalmol. 2018;29(3):267- 74.
27. Matas J, Llorenç V, Fonollosa A, Díaz-Valle D, Esquinas C, de la Maza MTS, et al. Systemic Regulatory T Cells and IL-6 as Prognostic Factors for Anatomical Improvement of Uveitic Macular Edema. Front Immunol. 2020;11:579005.
28. Bitossi A, Bettiol A, Silvestri E, Di Scala G, Bacherini D, Lopalco G, et al. Adalimumab Accounts for Long-Term Control of Noninfectious Uveitis Also in the Absence of Concomitant DMARD Treatment: A Multicenter Retrospective Study. Mediators Inflamm. 2019;2019:1623847.
29. Lee JT, Yates WB, Rogers S, Wakefield D, McCluskey P, Lim LL. Adalimumab for the treatment of refractory active and inactive non-infectious uveitis. Br J Ophthalmol. 2018; 102(12):1672-1678.
30. Matas J, Llorenç V, Fonollosa A, Esquinas C, Diaz-Valle D, Berasategui B, et al. Predictors for functional and anatomic outcomes in macular edema secondary to non-infectious uveitis. PloS One. 2019;14(1):e0210799.
31. Arevalo JF, Lasave AF, Al Jindan MY, Al Sabaani NA, Al-Mahmood AM, Al-Zahrani YA, et al. Uveitis in Behçet disease in a tertiary center over 25 years: the KKESH Uveitis Survey Study Group. Am J Ophthalmol. 2015;159(1):177-184.e1-2.
32. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H. Ocular features of Behcet's disease: an international collaborative study. Br J Ophthalmol. 2007;91(12):1579- 1582.
33. Taylor SRJ, Singh J, Menezo V, Wakefield D, McCluskey P, Lightman S. Behçet disease: visual prognosis and factors influencing the development of visual loss. Am J Ophthalmol. 2011;152(6):1059- 1066.
34. Vallet H, Seve P, Biard L, Baptiste Fraison J, Bielefeld P, Perard L, et al. Infliximab

Versus Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter Study From the French Uveitis Network. Arthritis Rheumatol. 2016;68(6):1522- 1530.

Table 1: Demographic and clinical characteristics of the 204 patients with refractory uveitic macular edema.

Parameter	**Total N=204**	**Anti-TNF-α N=149**	**TCZ N=55**	**p**
Age (median, IQR)	40 (28-58)	39 (25-57)	47 (32-64)	0.03
Male sex (N, %)	86 (42.2)	66 (44.3)	20 (36.4)	0.43
Geographic ancestry (N, %)				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 etiology (N, %)				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)	
Sarcoïdosis	15 (7.4)	14 (9.4)	1 (1.8)	
Juvenile idiopathic arthritis	12 (5.9)	10 (6.7)	2 (3.6)	
Vogt-Koyanagi-Harada	8 (3.9)	6 (4)	2 (3.6)	
Spondylo-arthritis	5 (2.4)	4 (2.7)	1 (1.8)	
Other	9 (4.4)	5 (3.4)	4 (7.3)	
Uveitis characteristics (N, %)				
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 ≥ 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	10 (4.9)	8 (5.4)	2 (3.6)	
intermediate	25 (12.3)	17 (11.4)	8 (14.5)	
posterior	65 (31.9)	46 (30.9)	19 (34.5)	
panuveitis	110 (53.9)	84 (56.4)	26 (47.3)	
Snellen visual acuity (RE)	20/50	20/50	20/63	
Median visual acuity (LogMAR) RE (IQR)	0.4 (0.2-0.7)	0.4 (0.2-0.7)	0.5 (0.2-1.0)	0.39
Snellen visual acuity (LE)	20/50	20/50	20/50	
Median visual acuity (LogMAR) LE (IQR)	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 (N, %)	183 (89.7)	134 (89.9)	49 (89.1)	0.86
Initial corticosteroid dose (mg/d) (IQR)	20 (10-30)	20 (10-30)	15 (8-20)	0.78
Concomitant treatment with immunosuppressive drugs (N, %)	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)	

Data are median [25-75 interquantile range], or number (percentage), Anti-TNF-α : Tumor Necrosis Factor alpha antagonist.

Table 2: Univariate analysis of factors with complete response, relapse and low visual acuity.

Parameter	Complete response		Relapse		Low vision	
	OR (95% CI)	**p value**	**HR (95% CI)**	**p value**	**OR (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 (years)	0.99 (0.98-1.01)	0.47	1.01 (1.00-1.02)	0.22	0.99 (0.98-1.01)	0.21
Etiologies		0.16		**0.012**		
Idiopathic uveitis	1		**1**		**1**	**0.021**
Behcet'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	
Sub-cutaneous	0.38 (0.10-1.42)		3.46 (0.22-55.8)		0.89 (0.23-3.42)	

OR: odds-ratio, HR: hazard-ratio, IQR: interquartile range.

Table 3: Adverse events occurring during biological therapies.

	Total	**Anti-TNF-α agents**		**Tocilizumab**
		Adalimumab	**Infliximab**	
Any adverse events (N,%)	42 (20.6)	13 (16.3)	22 (31.9)	7 (12.7)
Serious adverse events (N,%)	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 *(P.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
Non melanoma skin cancer	1 (4.5)	0	1 (8.3)	0
Hypersensitivity reaction	4 (18.2)	1 (14.3)	3 (25)	0
Auto-immune 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
Non-serious adverse events (N,%)	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

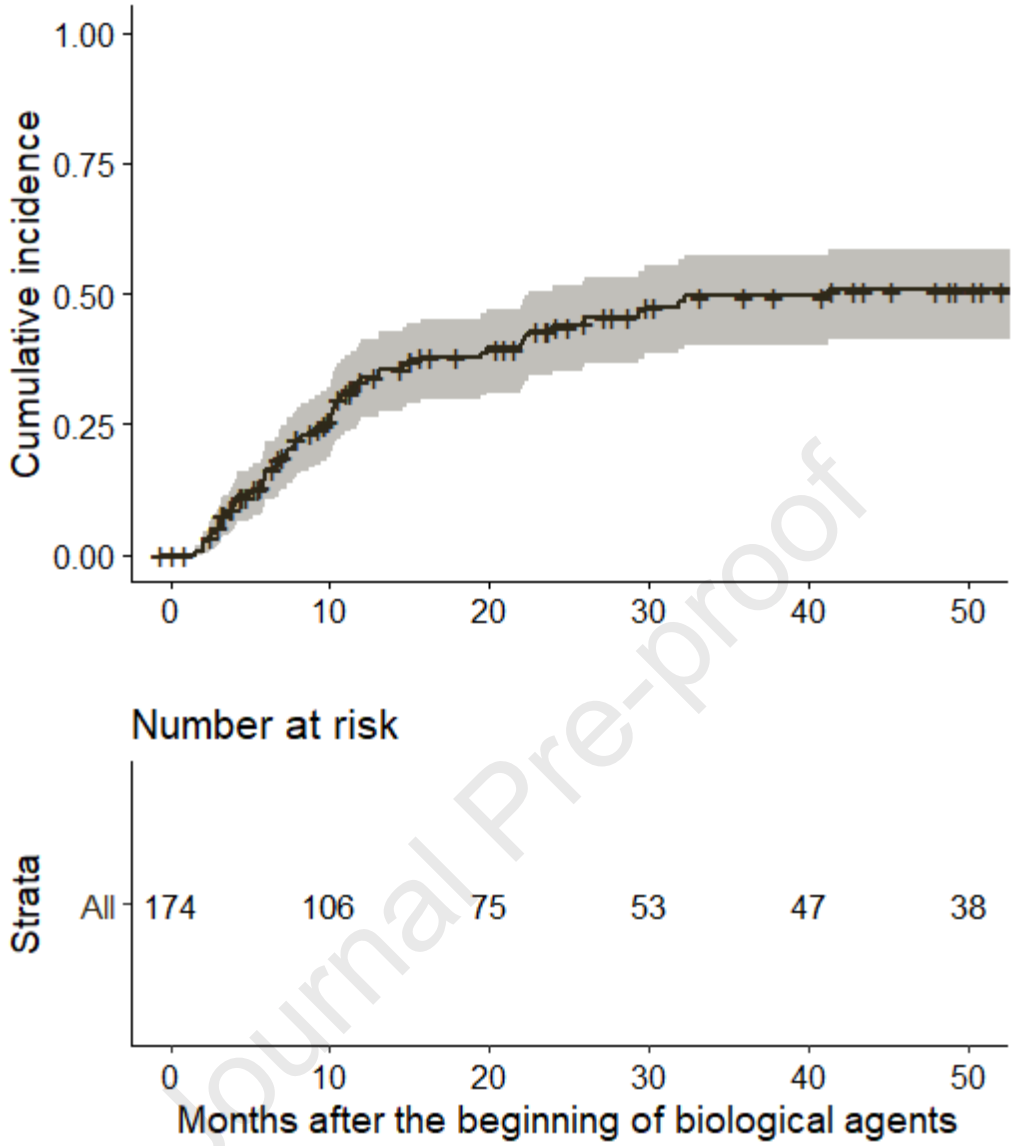


Figure 2: Cumulative incidence of relapse with biological agents.

Responses of CME

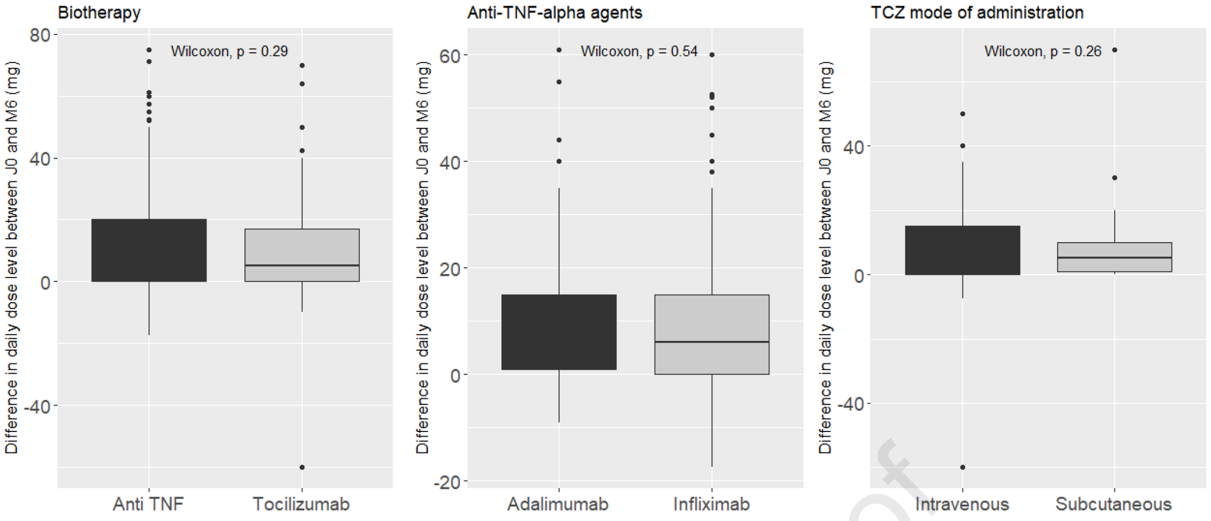
Variable		N	Odds ratio		p
Posterior uveitis	0	182		Reference	
	1	84		0.67 (0.35, 1.25)	0.22
Tocilizumab or anti-TNF	Anti TNF	216		Reference	
	Tocilizumab	50		2.10 (1.06, 4.06)	0.03

Relapse of CME

Variable		N	Hazard ratio		p
Uveitis etiology	Idiopathic	74		Reference	
	Behcet	33		0.40 (0.21, 0.77)	0.007
	Others	65		0.60 (0.36, 0.99)	0.046
Panuveitis	0	80		Reference	
	1	92		1.71 (0.72, 4.06)	0.224
Posterior uveitis	0	114		Reference	
	1	58		2.50 (1.03, 6.05)	0.043
Tocilizumab or anti-TNF	Anti TNF	160		Reference	
	Tocilizumab	12		0.76 (0.23, 2.51)	0.658

Low visual acuity

Variable		N	Odds ratio		p
Uveitis etiology	Idiopathic	106		Reference	
	Behcet	37		3.05 (1.38, 6.81)	0.006
	Others	96		1.41 (0.77, 2.60)	0.270
Tocilizumab or anti-TNF	Anti TNF	196		Reference	
	Tocilizumab	43		1.18 (0.56, 2.42)	0.648



In this multicenter observational study, 204 patients (149 treated with anti-TNF-α and 55 treated with had tocilizumab) with refractory uveitic macular edema were included. Tocilizumab was significantly associated with complete response (resolution of macular edema).