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## **Anti-TNF- $\alpha$ versus tocilizumab in the treatment of refractory uveitic macular edema: a multicenter study from the French Uveitis Network**

Mathilde Leclercq, Anaïs Andrillon, Georgina Maalouf, Pascal Sève, Philip Bielefeld, Julie Gueudry, Thomas Sené, Thomas Moulinet, Bénédicte Rouvière, Damien Sène, et al.

### ► To cite this version:

Mathilde Leclercq, Anaïs Andrillon, Georgina Maalouf, Pascal Sève, Philip Bielefeld, et al.. Anti-TNF- $\alpha$  versus tocilizumab in the treatment of refractory uveitic macular edema: a multicenter study from the French Uveitis Network. *Ophthalmology: Journal of The American Academy of Ophthalmology*, 2021, S0161-6420 (21), pp.00900-3. 10.1016/j.ophtha.2021.11.013 . hal-03478342

**HAL Id: hal-03478342**

**<https://hal.univ-lorraine.fr/hal-03478342>**

Submitted on 13 Dec 2021

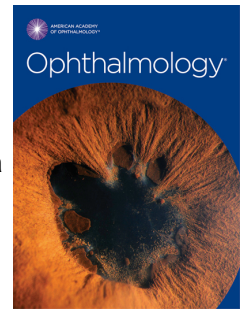
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# Journal Pre-proof



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PII: S0161-6420(21)00900-3

DOI: <https://doi.org/10.1016/j.ophtha.2021.11.013>

Reference: OPHTHA 11909

To appear in: *Ophthalmology*

Received Date: 18 June 2021

Revised Date: 1 November 2021

Accepted Date: 8 November 2021

Please cite this article as: Leclercq M, Andrillon A, Maalouf G, Sève P, Bielefeld P, Gueudry J, Sené T, Moulinet T, Rouvière B, Sène D, Desbois A-C, Domont F, Touhami S, El Chamieh C, Cacoub P, Bodaghi B, Biard L, Saadoun D, Anti-TNF- $\alpha$  versus tocilizumab in the treatment of refractory uveitic macular edema: a multicenter study from the French Uveitis Network., *Ophthalmology* (2021), doi: <https://doi.org/10.1016/j.ophtha.2021.11.013>.

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1 **Anti-TNF- $\alpha$  versus tocilizumab in the treatment of refractory**  
 2 **uveitic macular edema: a multicenter study from the French**  
 3 **Uveitis Network.**

4  
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41  
 42  
 43 **Key words:**

44 anti-TNF- $\alpha$  agents, tocilizumab, uveitic macular edema, efficacy, safety  
 45  
 46  
 47  
 48

49 **Words count:**

50 21 pages

51 3263 words

52 34 references

53 3 Tables

54 3 Figures

55

56

57 **Running head:** Anti-TNF- $\alpha$  alpha versus tocilizumab in refractory uveitic macular edema

58

59 **Financial Support: None.**

60 **No conflicting relationship exists for any author.**

61

62 **Highlights:**

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

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

66

## 67 Abstract

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

71 **Design:** Multicenter retrospective observational study.

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

74 **Methods:** Patients received anti-TNF- $\alpha$  agents [IFX 5 mg/kg at weeks 0, 2, 6 and every 4-6  
75 weeks (n=69) and ADA 40 mg/14 days (n=80)] and tocilizumab [8 mg/kg every 4 weeks  
76 intravenously (n=39) and 162 mg/week subcutaneously (n=16)].

77 **Main Outcome Measures:** Analysis of complete and partial response rates, relapse rate, low  
78 vision (visual acuity in at least one eye  $\geq 1$  LogMAR), corticosteroid sparing effect and adverse  
79 events at 6 months.

80 **Results:** 204 patients (median age of 40 years [28-58] with 42.2% of men) were included. Main  
81 etiologies of uveitis included Behçet's disease (17.2%), birdshot chorioretinopathy (11.3%) and  
82 sarcoidosis (7.4%). The overall response rate at 6 months was of 46.2% (21.8% of complete  
83 response) with anti-TNF- $\alpha$  agents and 58.5% (35.8% of complete response) with tocilizumab.  
84 In multivariate analysis, treatment with tocilizumab (OR 2.10 [95% CI 1.06–4.06], p=0.03) was  
85 independently associated with complete response of uveitic macular edema, compared to anti-  
86 TNF- $\alpha$  agents. Anti-TNF- $\alpha$  agents and tocilizumab did not differ significantly in terms of  
87 relapse rate (HR=1.00 [0.31-3.18], p=0.99) or occurrence of low vision (OR=1.02 [0.51-2.07],  
88 p=0.95) or corticosteroid-sparing effect (p=0.29). Adverse events were reported in 20.6% of  
89 patients, including 10.8% of serious adverse events.

90 **Conclusions:** Tocilizumab seems to improve complete response of uveitic macular edema  
91 compared to anti-TNF- $\alpha$  agents.

## 92 **Introduction**

93 Non-infectious inflammatory uveitis is a heterogeneous group of diseases, characterized  
94 by inflammation of intra-ocular structure. It can be associated with systemic autoimmune  
95 diseases or be sporadic of unknown etiology. With a prevalence of 121/100,000 persons (1),  
96 uveitis is one of the five common causes of visual loss in industrialized countries (2). Cataract,  
97 glaucoma and macular alterations account for the main ocular complications of uveitis (3,4).

98 Uveitic macular edema (uveitic ME) is related to the breakdown of the outer and/or the  
99 inner blood-retinal barrier secondary to chronic inflammation and secretion of pro-  
100 inflammatory factors such as TNF- $\alpha$  (tumor necrosis factor), prostaglandins and VEGF  
101 (vascular endothelial growth factor) (5,6). These pro-inflammatory factors result in an increase  
102 of permeability of the retinal pigment epithelium and the retinal vasculature (7,8). Uveitic ME  
103 is more common in patients with intermediate uveitis (25-70%), posterior uveitis (19-34%) and  
104 panuveitis (18-66%). Uveitic ME is responsible for a severe decrease of visual acuity in one-  
105 third of patients with posterior uveitis (9), supporting an effective therapeutic management.

106 Several treatments can be used for uveitic ME management. Local corticosteroids, with  
107 periocular injections or, mostly, intravitreal implants of corticosteroids, are usually proposed in  
108 cases of unilateral uveitic ME, absence of associated systemic disease or as an adjunct to  
109 systemic therapy (7). Intravitreal implants of dexamethasone (OZURDEX®) have been shown  
110 to improve visual acuity (VA) of more than 2 lines in 50% of patients. However, in a recent  
111 literature review, almost one third did not have any visual improvement despite a decrease of  
112 central foveal thickness (CFT) (10). Fluocinolone acetonide implant (RETISERT®) has also  
113 shown its efficacy in uveitis. Recently, Tomkins-Netzer et al. (11) reported that the cumulative  
114 percent of eyes with resolution of CME was 94% within the 7 years of follow-up, with a median  
115 time of resolution of one year. However, the cumulative percent of eyes with relapse of uveitic  
116 ME was 43%. Conventional immunosuppressive drugs such as mycophenolate mofetil,

117 methotrexate or azathioprine have shown their efficacy in the resolution of uveitic ME (12,13).  
118 Interestingly, systemic immunosuppressive drugs have shown their efficacy on uveitic ME  
119 resolution with fewer adverse events than corticosteroid implant (14). Biotherapies appear as  
120 an attractive option in the treatment of uveitic ME, though few data are available. Adalimumab  
121 (ADA), an anti-TNF- $\alpha$  antibody, has been approved by the Food and Drug Administration  
122 (FDA) and the European Medicine Agency (EMA) for the treatment of patients with non-  
123 infectious non-anterior uveitis in case of corticosteroid-dependency (15) or contraindication to  
124 corticosteroids (16). However, it is a priority to evaluate macular edema as a trial endpoint  
125 because it is a major cause of functional visual loss during uveitis. A Cochrane review (17)  
126 reported that no prospective study has focused on the resolution of uveitic ME with biologics.  
127 The efficacy of anti-TNF- $\alpha$  agents and tocilizumab (TCZ), an anti-IL6 receptor, in the  
128 resolution of macular edema has been suggested in few retrospective studies (18-20).

129 Data regarding factors associated with response to anti-TNF- $\alpha$  agents or TCZ are  
130 lacking in refractory ME in non-infectious uveitis. In the BIOVAS study (BIOtherapies in  
131 macular edema and retinal VASculitis) from the French uveitis network, our aim was to analyze  
132 the efficacy, as well as adverse events of anti-TNF- $\alpha$  agents and TCZ to control ocular  
133 inflammation and corticosteroid sparing effect in a large retrospective cohort of patients with  
134 refractory ME in non-infectious uveitis.

135

## 136 **Methods**

### 137 **Patients**

138 This was a multicenter retrospective observational study conducted in participating  
139 Internal Medicine and Ophthalmology departments of the French Uveitis Network between  
140 2018 and 2020. Adult patients with refractory uveitic ME were included. Refractory ME was  
141 defined as macular edema resistant to a first line therapy with systemic corticosteroids and/or

142 disease modifying anti-rheumatic drugs (DMARDs, i.e., mycophenolate mofetil, methotrexate,  
143 azathioprine etc) and which requires treatment escalation with anti-TNF- $\alpha$  agents (ADA and  
144 infliximab, IFX) or TCZ. Uveitic ME was defined by a CFT of  $> 300 \mu\text{m}$  measured with spectral  
145 domain optical coherence tomography (OCT) and the presence of intraretinal cystic spaces or  
146 subretinal fluid in the absence of choroidal neovascularization. Patients were excluded if they  
147 presented non-infectious uveitis without macular edema or macular edema unrelated to uveitis.  
148 Patients previously treated with intravitreal implants of dexamethasone within 6 months were  
149 excluded.

150 The study complied with the ethical principles of the Declaration of Helsinki. This study was  
151 approved by the local ethics committee of Pitié-Salpêtrière Hospital (Number: 1867484).  
152 Informed consent was not required as per French regulations for research on Humans due to  
153 the retrospective strictly observational nature of the study.

#### 154 155 Study treatment

156 IFX was administered intravenously at 5 mg/kg at week 0, 2, 6 and every 4-6 weeks, left at the  
157 discretion of the clinician. ADA was administered subcutaneously at 80 mg then 40 mg every  
158 2 weeks. TCZ was administered at 8 mg/kg every 4 weeks intravenously or at a dose of 162 mg  
159 every week subcutaneously. The choice of biotherapy was left at the discretion of the clinician.

#### 160 161 Data collection

162 Collected data included demographic characteristics (age, sex, date of diagnosis),  
163 treatment characteristics (concomitant treatment, corticosteroid dose, adverse events), uveitis  
164 characteristics (etiology, anatomic localization according to the Standardization of Uveitis  
165 Nomenclature [SUN] (21)), course of visual acuity (Snellen and LogMAR), evolution of  
166 anterior chamber cells according to SUN classification (21), evolution of vitreous haze grade



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

171

## 172 Study endpoints

173 The primary objective was the complete response of uveitic ME at 6 months. Complete  
174 response was defined as a complete resolution of uveitic ME (CFT  $\leq$  300  $\mu$ m with resolution  
175 of intraretinal cystic spaces) and a corticosteroid dosage of  $\leq$  10 mg/ day at 6 months, without  
176 intraocular inflammation (grade 0 for anterior chamber cells and vitreous haze (22)). Partial  
177 response was defined as an improvement of macular edema without complete resolution, an  
178 improvement of intraocular inflammation and a reduction of the initial corticosteroid dosage at  
179 6 months. Patients with complete resolution of uveitic ME with a corticosteroid dosage of  $>$  10  
180 mg/ day at 6 months were also considered as partial responders. The remaining patients were  
181 considered as non-responders.

182 Secondary end points included factors associated with relapse of uveitic ME, factors  
183 associated with low visual acuity and adverse events. Relapse was defined as an increase of  
184 macular thickness requiring a change in therapeutic strategy (increase of corticosteroid dose,  
185 intra-ocular corticosteroid injection, or another biotherapy) in at least one eye. Low vision was  
186 defined as visual acuity in at least one eye  $\geq$  20/200 (1 LogMAR).

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

191

## 192 Statistics

193 Data on categorical variables were summarized as number and percent and compared  
194 using Fisher's exact test. Data on continuous variables were summarized as the median and  
195 interquartile range (IQR) and were compared using Wilcoxon test or Kruskal-Wallis tests. For  
196 the evaluation of primary and secondary end points, each treatment line was considered per  
197 patient for univariate and multivariate analysis. Factors associated with complete response or  
198 low vision were assessed using logistic regression. Factors associated with relapse were  
199 assessed using Cox proportional hazards models. For both endpoints, an adjusted multivariate  
200 model was used with backward variable selection based on Akaike's information criterion.  
201 Clinically relevant variables were candidates for the stepwise selection and the treatment group  
202 variable was forced into the adjusted model. Cumulative incidences of relapse were estimated  
203 using Kaplan-Meier method. Statistical analyses were performed using R Studio Version 3.6.1  
204 and p values < 0.05 were considered to be statistically significant.

## 206 Results

207 Baseline data are summarized in **Table 1**. Two hundred and four patients (women  
208 [57.8%], with a median age [IQR] of 40 years old [28-58]) were included in the study: 149  
209 patients (73%) were treated with anti-TNF- $\alpha$  agents (80 with ADA and 69 with IFX) and 55  
210 patients (27%) received TCZ (39 intravenous and 16 subcutaneous). One hundred and ten  
211 (53.9%) patients had panuveitis and 77 patients (37%) had retinal vasculitis. The main  
212 etiologies of uveitis were Behçet's disease (35 patients, 17.2%), birdshot chorioretinopathy (23  
213 patients, 11.3%) and sarcoidosis (15 patients, 7.4%). One hundred and eighty-three patients  
214 (89.7%) and 82 patients (40.2%) received systemic corticosteroids or DMARDs, respectively,  
215 in combination with anti-TNF- $\alpha$  agents or TCZ. Patients treated with TCZ were significantly  
216 older (p=0.03) and uveitis etiologies were significantly different between the two groups

217 (p=0.03). Forty-two patients (76%) treated with TCZ had previously received anti-TNF- $\alpha$   
218 agents. Most of patients had been previously treated with DMARDs: 82% in the anti-TNF- $\alpha$   
219 group and 87% in the TCZ group (p=0.40). Median time [IQR] to follow-up was 74.5 months  
220 [37-137], with a median time [IQR] of 88 months [37-144], 72.5 months [39-131] and 76  
221 months [38-135] for IFX, ADA and TCZ, respectively. Median time from diagnosis of uveitis  
222 to introduction of biotherapy was 40 months [11.7-89.6] for anti-TNF- $\alpha$  agents and 29 months  
223 [9-60] for TCZ (p=0.15).

224

### 225 **Response of uveitic ME to treatment.**

226 A total of 280 lines of treatment were studied including 225 lines of anti-TNF- $\alpha$  agents  
227 (117 ADA/108 IFX) and 55 lines of TCZ. Complete response at 6 months was achieved in  
228 24.5% of whom 21.8% with anti-TNF- $\alpha$  agents and 35.8% with TCZ. ADA and IFX had similar  
229 complete response rate: 22.2% and 21.3% respectively.

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

234 Partial response was obtained in 24.1% of whom 24.4% with anti-TNF- $\alpha$  and 22.6%  
235 with TCZ.

236

### 237 **Relapse of uveitic ME.**

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

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

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

248

#### 249 **Low visual acuity.**

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

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

258

#### 259 **Corticosteroid sparing effect.**

260 Biological agents had a significant corticosteroid-sparing effect (**Figure 3**). The median  
261 [IQR] daily dose of prednisone was 19 mg [10-30] at the initiation of ADA compared to 10 mg  
262 [7.4-18.5] after 6 months of treatment (p<0.0001). For IFX, the median daily dose decreased  
263 from 20 mg [10-30] to 10 mg at 6 months [0-40] (p=0.0006). For TCZ, the median daily dose  
264 decreased from 15 mg [8-20] to 10 mg at 6 months [0-40] (p=0.0006). However, there was not

265 a significant difference for corticosteroid sparing between anti-TNF- $\alpha$  agents and TCZ  
266 (p=0.29), nor between ADA and IFX (p=0.54) and intravenous or subcutaneous TCZ (p=0.26).

267

### 268 **Adverse events.**

269 Adverse events occurred in 20.6% of patients and serious adverse events requiring  
270 treatment discontinuation were observed in 10.8% (**Table 3**). For anti-TNF- $\alpha$  agents, at least  
271 one adverse event occurred in 23.5%, with 12.8% of serious adverse events requiring treatment  
272 discontinuation. For TCZ, at least one adverse event occurred in 12.7%, with 5.5% of serious  
273 adverse events. No death occurred during follow-up. Most of adverse events were infections  
274 (54.5%), hypersensitivity reaction (18.2%) and auto-immune reaction (13.6%). Hospitalization  
275 was required for 3 infections (meningitis, *Pseudomonas aeruginosa* bacteremia and deep  
276 abscess). There was no opportunistic infection.

277

### 278 **Discussion**

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

286

287 Our study showed that TCZ improved the odds of complete response of uveitic ME by  
288 2 times compared with anti-TNF- $\alpha$  agents after 6 months of treatment. There was no significant  
289 difference between ADA and IFX efficacy nor between intravenous or subcutaneous TCZ. The

290 efficacy of both anti-TNF- $\alpha$  agents and TCZ (20) in uveitic ME resolution has been suggested  
291 in literature. In the prospective VISUAL III study, Shuler et al. showed that patients with active  
292 uveitis (n=242) had an improvement of CFT after 78 weeks of treatment with ADA whereas  
293 patients with inactive uveitis (n=129) had a stability of uveitic ME (23). Schaap-Fogler et al.  
294 found a significant decrease of CFT from 515  $\mu\text{m}$  to 262  $\mu\text{m}$  (p=0.04) after 6 months of  
295 treatment with anti-TNF- $\alpha$  agents. Similar results were observed with TCZ at 6 months (CFT  
296 decreased from 516  $\mu\text{m}$  to 271  $\mu\text{m}$  [p<0.001]) (24) or at 12 months (CFT decreased from 433  
297  $\mu\text{m}$  to 259  $\mu\text{m}$  [p<0.0001]) (25).

298 The efficacy of TCZ has mostly been shown for uveitic ME refractory to anti-TNF- $\alpha$   
299 agents (24,25). The originality of the BIOVAS study is to compare anti-TNF- $\alpha$  agents and TCZ  
300 for their efficacy to resolve uveitic ME in non-infectious uveitis. TCZ efficacy is supported by  
301 several experimental data from the literature. High levels of IL-6 were found in the aqueous  
302 humor of patients with uveitis (26). Recently, Matas et al. (27) showed a correlation between  
303 high serum levels of IL-6 and poor uveitic ME prognosis, whereas high levels of circulating  
304 lymphocytes T regulators were associated with uveitic ME resolution. Taken together, these  
305 results suggest that TCZ is a promising therapy for uveitic ME. Further prospective studies are  
306 warranted to define which biologics might be used as the first therapeutic option in sight-  
307 threatening uveitic ME. Therefore, the French Uveitis Network developed a prospective study  
308 comparing ADA and TCZ in sight-threatening uveitis (ClinicalTrial.gov NCT02929251).

309 Overall improvement of uveitic ME at 6 months of treatment was obtained in 46.2%  
310 with anti-TNF- $\alpha$  agents and 58.5% with TCZ. Complete and partial responses were observed  
311 in 21.8% and 24.4% of patients with anti-TNF- $\alpha$  agents and 35.8% and 22.6% with TCZ,  
312 respectively. In the BIOVAS study, complete response was defined as the resolution of uveitic  
313 ME, related to the new challenge to consider sight-threatening uveitis. Previous studies on ADA  
314 efficacy focused on the resolution of intra-ocular inflammation (anterior chamber and/or

315 vitreous haze) and found better outcomes, ranging from 70% (18),(28) to 90% (29) of complete  
316 response at 6 months. These results highlight the severity of uveitic ME and the difficulty of  
317 managing these patients, despite the current development of the therapeutic arsenal. Suhler et  
318 al. (23) in the VISUAL III study showed that 40% of patients with active uveitis did not respond  
319 to ADA.

320 Uveitic ME has been identified as a risk factor of visual loss in uveitis. Up to 30 to 42%  
321 of patients with uveitic ME had significant visual loss in a large study of uveitic ME (5). Matas  
322 et al. (30) highlighted bilateral uveitic ME, systemic disease and the presence of anterior  
323 chamber cells as good prognostic factors and showed that CFT was unfavorably associated with  
324 preserved vision. In our study, we showed that the risk of low visual acuity of uveitic ME was  
325 increased by 3 times in Behçet's uveitis. This risk has been reported in the literature, and  
326 estimated to be as high as 25% in different studies (31,32). In a retrospective study of 107  
327 Behçet's patients, the risk of visual loss at 10 years was 39% (33) and biologic agents were  
328 identified as protective factors. Our study highlights the poor visual prognosis of Behçet's  
329 disease despite therapeutic advances.

330 The adverse events observed with anti-TNF- $\alpha$  agents and TCZ in this study were  
331 consistent with the known safety profile of these biologics, and no new safety concerns were  
332 identified during longer-term exposure. No evidence of new or worsening of uveitis was  
333 observed. Serious adverse events were observed in 12.8% and 5.5% with anti- TNF-  $\alpha$  agents  
334 and TCZ, respectively. These results are similar to those of the VISUAL studies where 11.7%  
335 (15), 9.6% (16) and 19% (23) of serious adverse events were reported. An increased risk of  
336 serious adverse events with IFX was previously reported (34). For TCZ, Vegas-Ravenga et al.  
337 (25) reported three adverse events (nausea, viral conjunctivitis and bullous impetigo) in 25  
338 patients with uveitis during 12.7 months of follow-up. In the prospective STOP-uveitis study,

339 two of the 37 patients developed low absolute neutrophil counts, requiring treatment  
340 discontinuation for one of them (20).

341 The choice of biotherapy was up to the clinician. A potential bias in our work was a  
342 temporal bias. Indeed, anti-TNF- $\alpha$  agents were the first biotherapy used in the management of  
343 uveitis, before TCZ (18). In the BIOVAS study, the median year of introduction of anti-TNF-  
344  $\alpha$  agents was 2014 [2011-2017] compared to 2018 [2017-2018] for TCZ ( $p < 0.0001$ ). This time  
345 bias may have influenced the results, in support of anti-TNF- $\alpha$  agents. Moreover, in our study,  
346 76% of the patients treated with TCZ had previously been treated with anti-TNF- $\alpha$  agents, but  
347 without success, suggesting more severe disease. Despite this severity and the temporal bias,  
348 TCZ appeared to be more effective.

349 The comparison of our two groups shows a significant difference for age (older patients  
350 in the TCZ group) and uveitis etiologies. Seventy-six percent of the patients in the TCZ group  
351 were previously treated with anti-TNF- $\alpha$  agents. Thus, it was expected that patients in this group  
352 would be older. Concerning the etiological diagnoses, we did not perform subgroup studies.  
353 Further studies comparing the two biotherapies according to uveitis etiologies (i.e. Behçet's  
354 disease) are ongoing. However, there was no significant difference between the two groups,  
355 concerning initial ophthalmologic characteristics (visual acuity, ocular inflammation, retinal  
356 vasculitis), thus allowing comparison of ophthalmic efficacy for the current episode.

357 We acknowledge some limitations in this study. Our analysis was performed as a  
358 retrospective review. We were unable to collect complete longitudinal data on patients who  
359 were seen only on an intermittent basis. Prospective enrollment and data collection from the  
360 time of diagnosis would have been ideal but more difficult to achieve with rare diseases.  
361 Although the present study only compared anti-TNF- $\alpha$  agents and TCZ based on observational  
362 non-randomized observations, we used a logistic regression approach to minimize a potential  
363 confounding bias.



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

368

369

370 Acknowledgments

371 We are grateful to Nikki Sabourin-Gibbs, Rouen University Hospital, for her help in editing the  
372 manuscript.

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

376

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

378

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

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

Parameter	Total N=204	Anti-TNF- $\alpha$ 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)	
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	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 $\geq 1$ )	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 $\geq 1$ LogMAR	58 (31.7)	42 (28.2)	16 (29.1)	0.69
Adalimumab		18 (42.9)		
Infliximab		24 (57.1)		
Central foveal thickness ( $\mu\text{m}$ )	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 interquartile range], or number (percentage), Anti-TNF- $\alpha$  : Tumor Necrosis Factor alpha antagonist.

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

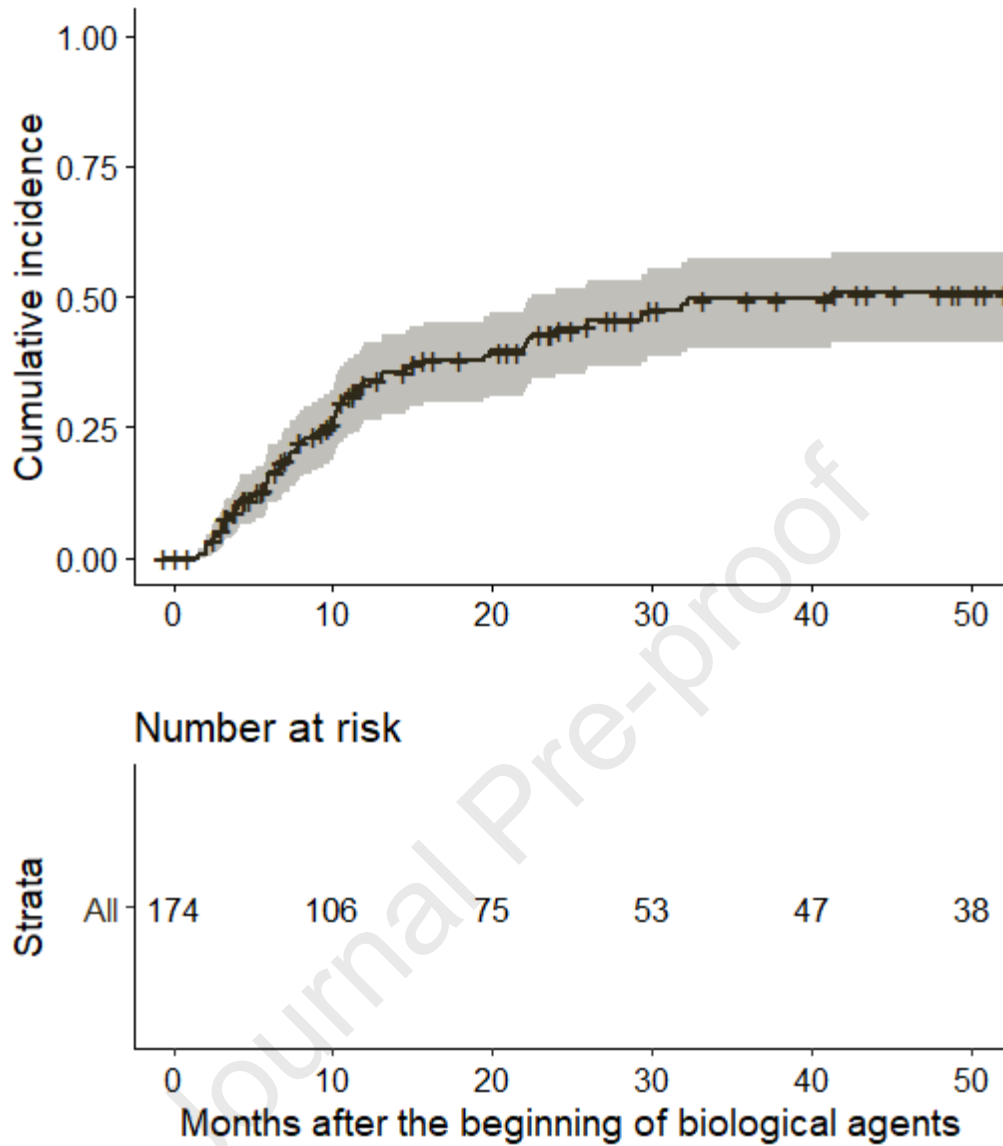
Parameter	Complete response		Relapse		Low vision	
	OR (95% CI)	p value	HR (95% CI)	p value	OR (95% CI)	p value
Male sex	0.87 (0.49-1.52)	0.62	1.17 (0.75-1.84)	0.49	0.91 (0.52-1.58)	0.74
Age (years)	0.99 (0.98-1.01)	0.47	1.01 (1.00-1.02)	0.22	0.99 (0.98-1.01)	0.21
Etiologies		0.16		<b>0.012</b>		
Idiopathic uveitis	1		1		1	<b>0.021</b>
Behcet's disease	0.73 (0.29-1.84)		<b>0.42 (0.22-0.81)</b>		2.96 (1.38-6.38)	
Others	1.54 (0.86-2.78)		<b>0.59 (0.36-0.96)</b>		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	<b>1.56 (0.98-2.49)</b>	<b>0.062</b>	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		<b>0.027</b>		0.99		0.95
Anti-TNF- $\alpha$ agents	1		1		1	
Tocilizumab	<b>2.08 (1.09-3.99)</b>		1.00 (0.31-3.18)		1.02 (0.51-2.07)	
Patients treated with anti-TNF- $\alpha$ agents		0.87		<b>0.0007</b>		<b>0.024</b>
Adalimumab	1		1		1	
Infliximab	0.95 (0.50-1.79)		<b>0.43 (0.27-0.70)</b>		<b>2.01 (1.10-3.67)</b>	
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- $\alpha$ agents		Tocilizumab
		Adalimumab	Infliximab	
<b>Any adverse events (N,%)</b>	42 (20.6)	13 (16.3)	22 (31.9)	7 (12.7)
<b>Serious adverse events (N,%)</b>	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 ( <i>P.Aeruginosa</i> )	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
<b>Non-serious adverse events (N,%)</b>	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

Detailed description: This forest plot displays Odds Ratios (OR) and 95% Confidence Intervals (CI) for two variables. For Posterior uveitis, the reference group (0) has an OR of 1.0, while group 1 has an OR of 0.67 (95% CI: 0.35, 1.25) with a p-value of 0.22. For Tocilizumab or anti-TNF treatment, the reference group (Anti TNF) has an OR of 1.0, while the Tocilizumab group has an OR of 2.10 (95% CI: 1.06, 4.06) with a p-value of 0.03. The x-axis is logarithmic, ranging from 0.5 to 2.0.

## Relapse of CME

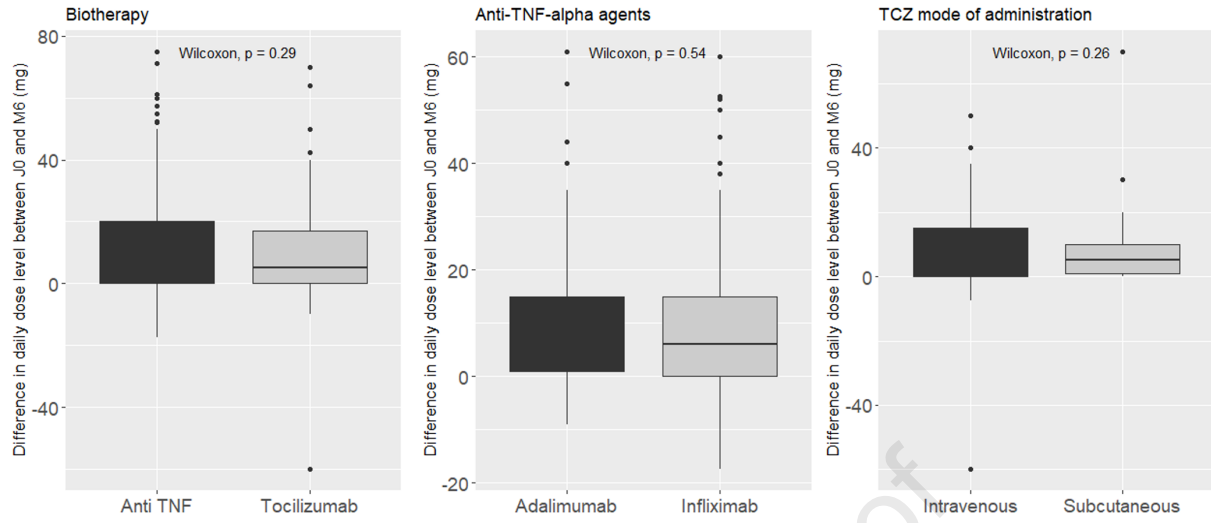
Variable		N	Hazard ratio	p
Uveitis etiology	Idiopathic	74	Reference	
	Behcet	33	0.40 (0.21, 0.77)	0.007
	Others	65	0.60 (0.36, 0.99)	0.046
Panuveitis	0	80	Reference	
	1	92	1.71 (0.72, 4.06)	0.224
Posterior uveitis	0	114	Reference	
	1	58	2.50 (1.03, 6.05)	0.043
Tocilizumab or anti-TNF	Anti TNF	160	Reference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

Detailed description: This forest plot displays Hazard Ratios (HR) and 95% Confidence Intervals (CI) for three variables. For Uveitis etiology, Idiopathic is the reference (HR 1.0). Behcet has an HR of 0.40 (95% CI: 0.21, 0.77) with p=0.007. Others have an HR of 0.60 (95% CI: 0.36, 0.99) with p=0.046. For Panuveitis, group 0 is the reference (HR 1.0). Group 1 has an HR of 1.71 (95% CI: 0.72, 4.06) with p=0.224. For Posterior uveitis, group 0 is the reference (HR 1.0). Group 1 has an HR of 2.50 (95% CI: 1.03, 6.05) with p=0.043. For Tocilizumab or anti-TNF treatment, Anti TNF is the reference (HR 1.0). Tocilizumab has an HR of 0.76 (95% CI: 0.23, 2.51) with p=0.658. The x-axis is logarithmic, ranging from 0.2 to 5.0.

## 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

Detailed description: This forest plot displays Odds Ratios (OR) and 95% Confidence Intervals (CI) for two variables. For Uveitis etiology, Idiopathic is the reference (OR 1.0). Behcet has an OR of 3.05 (95% CI: 1.38, 6.81) with p=0.006. Others have an OR of 1.41 (95% CI: 0.77, 2.60) with p=0.270. For Tocilizumab or anti-TNF treatment, Anti TNF is the reference (OR 1.0). Tocilizumab has an OR of 1.18 (95% CI: 0.56, 2.42) with p=0.648. The x-axis is logarithmic, ranging from 1 to 5.0.



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

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