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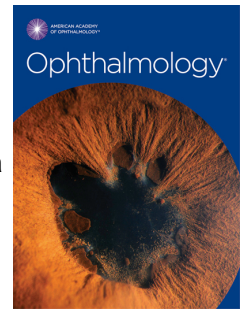
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1 **Anti-TNF- α versus tocilizumab in the treatment of refractory**
 2 **uveitic macular edema: a multicenter study from the French**
 3 **Uveitis Network.**

4
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62 **Highlights:**

63 Tocilizumab tends to be more effective than anti-TNF- α 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- α 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- α 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 ≥ 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- α 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- α agents. Anti-TNF- α 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- α 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- α (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- α 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- α 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- α 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- α 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- α 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 μ 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- α 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- α 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- α
218 agents. Most of patients had been previously treated with DMARDs: 82% in the anti-TNF- α
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- α 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- α 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- α 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- α agents (**Figure 1**).

234 Partial response was obtained in 24.1% of whom 24.4% with anti-TNF- α 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- α 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- α
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- α 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- α 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- α 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- α 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- α 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- α 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- α 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 μm to 262 μm (p=0.04) after 6 months of
295 treatment with anti-TNF- α agents. Similar results were observed with TCZ at 6 months (CFT
296 decreased from 516 μm to 271 μm [p<0.001]) (24) or at 12 months (CFT decreased from 433
297 μm to 259 μm [p<0.0001]) (25).

298 The efficacy of TCZ has mostly been shown for uveitic ME refractory to anti-TNF- α
299 agents (24,25). The originality of the BIOVAS study is to compare anti-TNF- α 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- α agents and 58.5% with TCZ. Complete and partial responses were observed
311 in 21.8% and 24.4% of patients with anti-TNF- α 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- α 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- α 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- α 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 α 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- α agents. Moreover, in our study,
346 76% of the patients treated with TCZ had previously been treated with anti-TNF- α 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- α 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- α 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- α 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

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372 manuscript.

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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383 **Bibliography:**

- 384 1. Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, et al. Prevalence of
385 Noninfectious Uveitis in the United States: A Claims-Based Analysis. *JAMA Ophthalmol.*
386 2016;134(11):1237- 1245.
- 387 2. Tsirouki T, Dastiridou A, Symeonidis C, Tounakaki O, Brazitikou I, Kalogeropoulos
388 C, et al. A Focus on the Epidemiology of Uveitis. *Ocul Immunol Inflamm.* 2018;26(1):2- 16.
- 389 3. Dick AD, Tundia N, Sorg R, Zhao C, Chao J, Joshi A, et al. Risk of Ocular
390 Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or
391 Panuveitis. *Ophthalmology.* 2016;123(3):655- 662.
- 392 4. Prieto-Del-Cura M, González-Guijarro JJ. Risk factors for ocular complications in
393 adult patients with uveitis. *Eur J Ophthalmol.* 2020;30(6):1381- 1389.
- 394 5. Massa H, Pipis SY, Adewoyin T, Vergados A, Patra S, Panos GD. Macular edema
395 associated with non-infectious uveitis: pathophysiology, etiology, prevalence, impact and
396 management challenges. *Clin Ophthalmol Auckl NZ.* 2019;13:1761- 1777.
- 397 6. de Smet MD. Insights into the Physiopathology of Inflammatory Macular Edema. *Dev*
398 *Ophthalmol.* 2017;58:168- 177.
- 399 7. Koronis S, Stavrakas P, Balidis M, Kozeis N, Tranos PG. Update in treatment of
400 uveitic macular edema. *Drug Des Devel Ther.* 2019;13:667- 680.
- 401 8. Touhami S, Beguier F, Augustin S, Charles-Messance H, Vignaud L, Nandrot EF, et
402 al. Chronic exposure to tumor necrosis factor alpha induces retinal pigment epithelium cell
403 dedifferentiation. *J Neuroinflammation.* 2018;15(1):85.
- 404 9. Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. *Eye Lond*
405 *Engl.* 2016;30(10):1277- 1292.
- 406 10. Massa H, Georgoudis P, Panos GD. Dexamethasone intravitreal implant
407 (OZURDEX®) for macular edema secondary to noninfectious uveitis: a review of the
408 literature. *Ther Deliv.* 2019;10(6):343- 351.
- 409 11. Tomkins-Netzer O, Lightman SL, Burke AE, Sugar EA, Lim LL, Jaffe GJ, et al.
410 Seven-Year Outcomes of Uveitic Macular Edema: The Multicenter Uveitis Steroid Treatment
411 Trial and Follow-up Study Results. *Ophthalmology.* 2021;128(5):719-728.
- 412 12. Doycheva D, Zierhut M, Blumenstock G, Stuebiger N, Deuter C. Mycophenolate
413 mofetil in the therapy of uveitic macular edema--long-term results. *Ocul Immunol Inflamm.*
414 2012;20(3):203- 211.
- 415 13. Rathinam SR, Babu M, Thundikandy R, Kanakath A, Nardone N, Esterberg E, et al. A
416 randomized clinical trial comparing methotrexate and mycophenolate mofetil for
417 noninfectious uveitis. *Ophthalmology.* 2014;121(10):1863- 1870.
- 418 14. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and
419 Follow-up Study Research Group, Kempen JH, Altaweel MM, Holbrook JT, Sugar EA,
420 Thorne JE, et al. Association Between Long-Lasting Intravitreal Fluocinolone Acetonide
421 Implant vs Systemic Anti-inflammatory Therapy and Visual Acuity at 7 Years Among
422 Patients With Intermediate, Posterior, or Panuveitis. *JAMA.* 2017;317(19):1993- 2005.
- 423 15. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, et al.
424 Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med.*
425 2016;375(10):932- 943.
- 426 16. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al.
427 Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis
428 controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised,
429 placebo-controlled phase 3 trial. *The Lancet.* 2016;388(10050):1183- 1192.
- 430 17. Barry RJ, Tallouzi MO, Bucknall N, Mathers JM, Murray PI, Calvert MJ, et al. Anti-
431 tumour necrosis factor biological therapies for the treatment of uveitic macular oedema
432 (UMO) for non-infectious uveitis. *Cochrane Database Syst Rev.* 2018;12:CD012577.

- 433 18. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, Cordero-Coma M, Ortega G, Ortego
434 N, et al. Treatment of Refractory Uveitis with Adalimumab: A Prospective Multicenter Study
435 of 131 Patients. *Ophthalmology*. 2012;119(8):1575- 1581.
- 436 19. Lejoyeux R, Diwo E, Vallet H, Saadoun D, Tezenas du Montcel S, Bodaghi B, et al.
437 Infliximab and Adalimumab in Uveitic Macular Edema. *Ocul Immunol Inflamm*.
438 2018;26(7):991- 996.
- 439 20. Sepah YJ, Sadiq MA, Chu DS, Dacey M, Gallemore R, Dayani P, et al. Primary
440 (Month-6) Outcomes of the STOP-Uveitis Study: Evaluating the Safety, Tolerability, and
441 Efficacy of Tocilizumab in Patients with Non-Infectious Uveitis. *Am J Ophthalmol*.
442 2017;183:71-80.
- 443 21. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature
444 (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data.
445 Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509- 516.
- 446 22. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal
447 inflammatory activity in intermediate and posterior uveitis. *Ophthalmology*.
448 1985;92(4):467- 471.
- 449 23. Suhler EB, Adán A, Brézin AP, Fortin E, Goto H, Jaffe GJ, et al. Safety and Efficacy
450 of Adalimumab in Patients with Noninfectious Uveitis in an Ongoing Open-Label Study:
451 VISUAL III. *Ophthalmology*. 2018;125(7):1075- 1087.
- 452 24. Mesquida M, Molins B, Llorenç V, Hernández MV, Espinosa G, Sainz de la Maza M,
453 et al. Twenty-four month follow-up of tocilizumab therapy for refractory uveitis-related
454 macular edema. *Retina Phila Pa*. 2017;38(7):1361-1370.
- 455 25. Vegas-Revenga N, Calvo-Río V, Mesquida M, Adán A, Hernández MV, Beltrán E, et al.
456 Anti-il6-r tocilizumab in refractory and non-infectious uveitic cystoid macular edema.
457 Multicenter study of 25 patients. *Am J Ophthalmol*. 2019;200:85-94.
- 458 26. Weinstein JE, Pepple KL. Cytokines in uveitis. *Curr Opin Ophthalmol*.
459 2018;29(3):267- 74.
- 460 27. Matas J, Llorenç V, Fonollosa A, Díaz-Valle D, Esquinas C, de la Maza MTS, et al.
461 Systemic Regulatory T Cells and IL-6 as Prognostic Factors for Anatomical Improvement of
462 Uveitic Macular Edema. *Front Immunol*. 2020;11:579005.
- 463 28. Bitossi A, Bettioli A, Silvestri E, Di Scala G, Bacherini D, Lopalco G, et al.
464 Adalimumab Accounts for Long-Term Control of Noninfectious Uveitis Also in the Absence
465 of Concomitant DMARD Treatment: A Multicenter Retrospective Study. *Mediators Inflamm*.
466 2019;2019:1623847.
- 467 29. Lee JT, Yates WB, Rogers S, Wakefield D, McCluskey P, Lim LL. Adalimumab for
468 the treatment of refractory active and inactive non-infectious uveitis. *Br J Ophthalmol*. 2018;
469 102(12):1672-1678.
- 470 30. Matas J, Llorenç V, Fonollosa A, Esquinas C, Diaz-Valle D, Berasategui B, et al.
471 Predictors for functional and anatomic outcomes in macular edema secondary to non-
472 infectious uveitis. *PloS One*. 2019;14(1):e0210799.
- 473 31. Arevalo JF, Lasave AF, Al Jindan MY, Al Sabaani NA, Al-Mahmood AM, Al-
474 Zahrani YA, et al. Uveitis in Behçet disease in a tertiary center over 25 years: the KKESH
475 Uveitis Survey Study Group. *Am J Ophthalmol*. 2015;159(1):177-184.e1-2.
- 476 32. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H. Ocular features of
477 Behçet's disease: an international collaborative study. *Br J Ophthalmol*.
478 2007;91(12):1579- 1582.
- 479 33. Taylor SRJ, Singh J, Menezo V, Wakefield D, McCluskey P, Lightman S. Behçet
480 disease: visual prognosis and factors influencing the development of visual loss. *Am J*
481 *Ophthalmol*. 2011;152(6):1059- 1066.
- 482 34. Vallet H, Seve P, Biard L, Baptiste Fraison J, Bielefeld P, Perard L, et al. Infliximab

483 Versus Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter
484 Study From the French Uveitis Network. *Arthritis Rheumatol.* 2016;68(6):1522- 1530.
485
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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- 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)	
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 ≥ 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 interquartile range], or number (percentage), Anti-TNF- α : 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		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 (<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
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

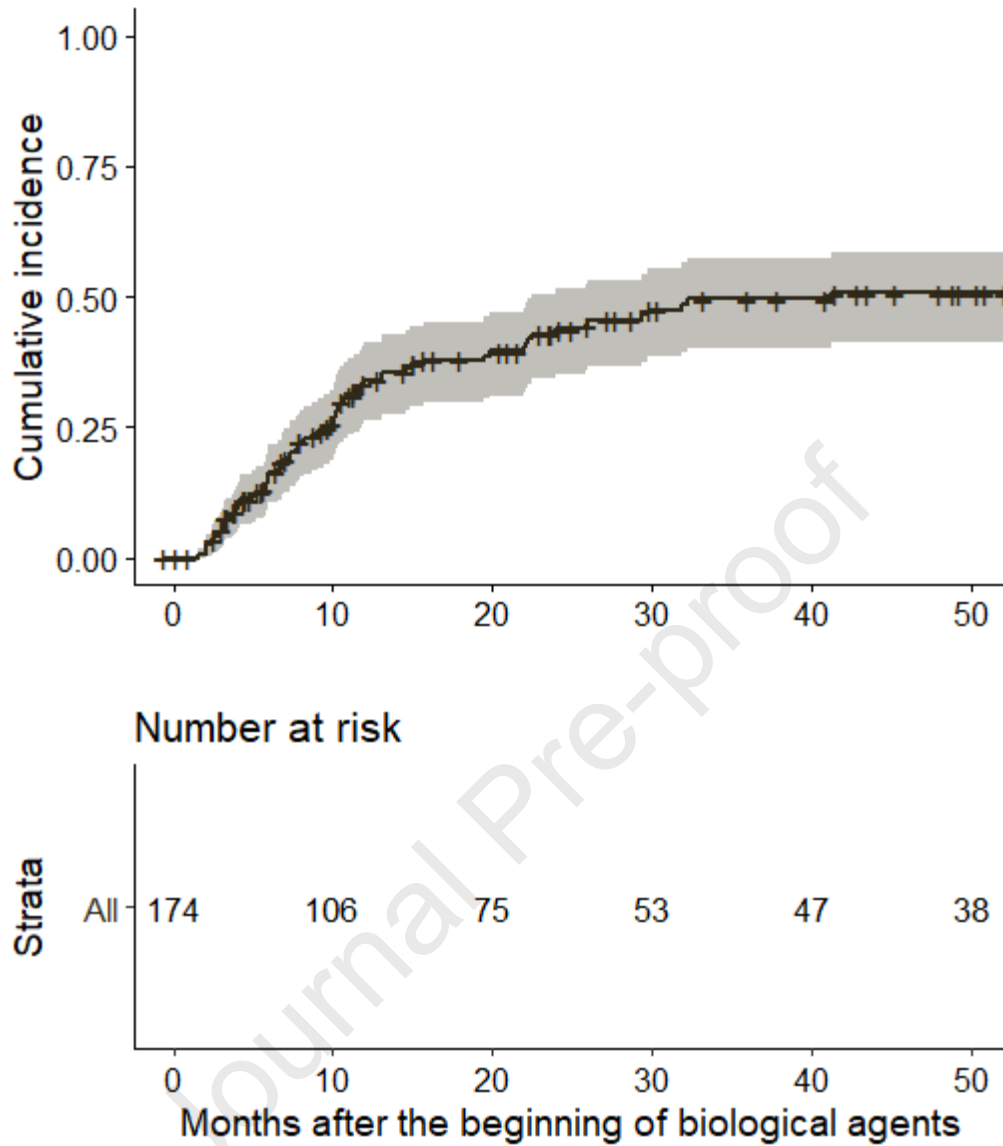


Figure 2: Cumulative incidence of relapse with biological agents.

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

Detailed description: This forest plot displays the Odds ratios for two variables: Posterior uveitis and Tocilizumab or anti-TNF. The x-axis represents the Odds ratio on a logarithmic scale from 0.5 to 2. A vertical dashed line is at 1.0. For Posterior uveitis, the Odds ratio for category 1 is 0.67 (95% CI 0.35, 1.25) with a p-value of 0.22. For Tocilizumab or anti-TNF, the Odds ratio for Tocilizumab is 2.10 (95% CI 1.06, 4.06) with a p-value of 0.03.

Relapse of CME

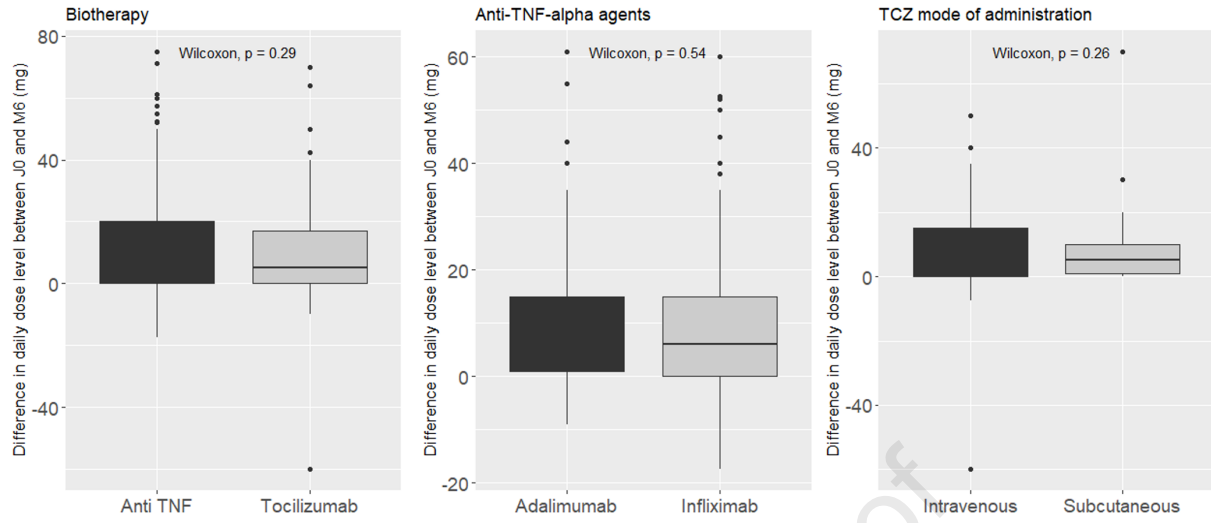
Variable		N	Hazard ratio	p
Uveitis etiology	Idiopathic	74	Reference	
	Behcet	33	0.40 (0.21, 0.77)	0.007
	Others	65	0.60 (0.36, 0.99)	0.046
Panuveitis	0	80	Reference	
	1	92	1.71 (0.72, 4.06)	0.224
Posterior uveitis	0	114	Reference	
	1	58	2.50 (1.03, 6.05)	0.043
Tocilizumab or anti-TNF	Anti TNF	160	Reference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

Detailed description: This forest plot displays the Hazard ratios for three variables: Uveitis etiology, Panuveitis, and Posterior uveitis. The x-axis represents the Hazard ratio on a logarithmic scale from 0.2 to 5. A vertical dashed line is at 1.0. For Uveitis etiology, Behcet has a Hazard ratio of 0.40 (95% CI 0.21, 0.77) with a p-value of 0.007, and Others has a Hazard ratio of 0.60 (95% CI 0.36, 0.99) with a p-value of 0.046. For Panuveitis, category 1 has a Hazard ratio of 1.71 (95% CI 0.72, 4.06) with a p-value of 0.224. For Posterior uveitis, category 1 has a Hazard ratio of 2.50 (95% CI 1.03, 6.05) with a p-value of 0.043. For Tocilizumab or anti-TNF, Tocilizumab has a Hazard ratio of 0.76 (95% CI 0.23, 2.51) with a p-value of 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

Detailed description: This forest plot displays the Odds ratios for two variables: Uveitis etiology and Tocilizumab or anti-TNF. The x-axis represents the Odds ratio on a logarithmic scale from 1 to 5. A vertical dashed line is at 1.0. For Uveitis etiology, Behcet has an Odds ratio of 3.05 (95% CI 1.38, 6.81) with a p-value of 0.006, and Others has an Odds ratio of 1.41 (95% CI 0.77, 2.60) with a p-value of 0.270. For Tocilizumab or anti-TNF, Tocilizumab has an Odds ratio of 1.18 (95% CI 0.56, 2.42) with a p-value of 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).

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