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ABSTRACT

Objective: To compare the efficacy and safety of Disease-modifying antirheumatic drugs (DMARDs) and anti-TNF-α agents in patients with non-infectious non-anterior uveitis.
Methods: Single center retrospective study including adult patients with non-infectious intermediate, posterior or pan-uveitis. Outcomes were compared between patients treated with DMARDs or anti-TNF-α agents. The primary outcome was treatment failure or occurrence of serious adverse events. Treatment failure was determined by ophthalmologic criteria.
Results: Seventy-three patients were included, mostly female (52%). Among them, 39 were treated with DMARDs and 34 with anti-TNF-α agents. The main uveitis causes were idiopathic (30%), birdshot chorio-retinopathy (25%), sarcoidosis (16%) and Behçet's disease (14%). The primary outcome was observed in 56% of patients treated with anti-TNF-α agents versus 59% of patients treated with DMARDs ($p = 0.82$). Median time to observe the primary outcome was 16 months (anti-TNF-α group) versus 21 months ($p = 0.52$). There was no significant difference between the two groups in terms of treatment failure, corticosteroid sparing effect, visual acuity improvement or adverse events. Earlier control of ocular inflammation was achieved with anti-TNF-α agents than with DMARDs ($p = 0.006$). In relapsing patients, anti-TNF-α agents allowed better corticosteroid sparing ($p = 0.06$).
Conclusion: DMARDs could still be used as first-line therapy for non-infectious non-anterior uveitis after corticosteroid therapy. However, anti-TNF-α agents could be proposed as an alternative in cases of severe inflammation or initial high level of steroid dependency.

1. Introduction

Uveitis is an inflammatory disease of the uvea, also involving retina inflammation and papillitis [1]. In developed countries, most uveitis cases are secondary to inflammation (91%) without infection. The prevalence of non-infectious non-anterior uveitis is 23/100,000 persons [2]. Inflammation can be limited to the eye, such as in birdshot chorioretinopathy [3] or multifocal choroiditis [4], or can be secondary to a systemic disease, such as Behçet's disease or sarcoidosis [5]. Uveitis classification is based on its localization [6]. Anterior uveitis corresponds to an inflammation of ciliary bodies and iris, and due to its localization, is most often managed with topical treatment in adults. For unilateral intermediate, posterior and pan-uveitis, peribulbar or intraocular corticosteroid injections can be proposed [7]. When both eyes are involved or complications related to topical treatment appear, systemic treatment is warranted. Corticosteroid represents the first-line of treatment. However, when a relapse occurs or in case of corticosteroid dependency, other treatments are needed. Currently, immunosuppressive drugs such as DMARDs (Disease-modifying antirheumatic drugs) are used as first-line therapy. In the SITE (Systemic immunosuppressive therapy for eye diseases) cohort study [8], methotrexate [9], azathioprine [10] and mycophenolate mofetil [11] showed their efficacy to control intra-ocular inflammation, to improve visual acuity and to allow a corticosteroid sparing effect. Anti-TNF-α agents,

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such as adalimumab and infliximab, appear to be effective too. In the two multicenter randomized controlled trials, VISUAL I [12] and VISUAL II [13], the median time to treatment failure was significantly shorter for patients receiving placebo than those treated with adalimumab ($p < 0.001$).

However, the therapeutic strategy between DMARDs and anti-TNF-α agents has not been clearly established.

The aim of our study was to compare the efficacy and safety of DMARDs and anti-TNF-α agents in patients with non-infectious non-anterior uveitis.

2. Materials and methods

We conducted a single center retrospective study in the Internal Medicine and the Ophthalmology Departments of a French university hospital between 2014 and 2018. Adult patients with non-infectious non-anterior uveitis, treated with anti-TNF-α agents (adalimumab or infliximab) or DMARDs (azathioprine, methotrexate, mycophenolate mofetil), were included. Only the initial treatment line of DMARDs or anti-TNF-α agents was studied. Patients treated with anti-TNF-α agents could have been previously treated with DMARDs. In the anti-TNF-α group, patients who never received DMARDs (naïve patients) were distinguished from patients previously treated with DMARDs. The choice of anti-TNF-α agents as first-line therapy was based on the initial severity of ophthalmologic characteristics, uveitis etiology and physician's assessment. Patients only treated with corticosteroids, non-anti-TNF-α agents or interferon alpha-2a were excluded.

Collected data included demographic characteristics, i.e. age, sex, date of diagnosis, uveitis characteristics, i.e. etiology, anatomic localization and evaluation of intra-ocular inflammation according to the Standardization of Uveitis Nomenclature [1] and the Nussenblatt grading scale [14], presence of retinal vasculitis or cystoid macular edema at diagnosis, at the time of initiation of DMARDs or anti-TNF-α agents and at the end of follow-up. Characteristics of treatment, i.e. type, indication, posology, date of introduction, previous treatments, and evolution of corticosteroid dose were also collected.

The primary outcome was composite, encompassing both treatment failure and serious adverse events. Treatment failure was defined as: 1) two-step increase in anterior chamber cell [1], or 2) two-step increase in vitreous haze grade [14], or 3) worsening of the best corrected visual acuity by 15 or more letters on the Early Treatment Diabetic Retinopathy Study chart, or 4) persistence or worsening or appearance of cystoid macular edema, or 5) persistence or worsening or appearance of retinal vasculitis. Cystoid macular edema was characterized by CFT (central foveal thickness) > 300 µm with intraretinal cystic spaces measured with OCT (optical coherence tomography, Cirrus HD-OCT Carl Zeiss Meditec, Dublin, CA). Retinal vasculitis was defined on fluorescein angiography. Anti-TNF-α agents or DMARDs were not systematically withdrawn in cases of treatment failure, add-on therapy could be used such as corticosteroid intra- or peri-ocular injection.

Adverse events were defined as serious if treatment discontinuation was needed.

Secondary efficacy outcomes were: improvement of visual acuity, evolution of intraocular inflammation assessed by ocular quiescence (anterior chamber cell $\leq 0.5+$ and vitreous haze grade $\leq 0.5+$), corticosteroid sparing effect and non-serious adverse events.

The study was approved by the local ethics committee (E2019-63).

2.1. Statistics

Data on categorical variables were compared using Fisher's exact test, or, Chi 2 test. Data on continuous variables were summarized as the median and interquartile range (IQR) and were compared using Mann Whitney test. The median time to observe the primary outcome was calculated using Kaplan-Meier method and was compared using Log Rank test. Event-free survival was defined as the percentage of patients in whom the primary outcome was not observed. Evolution of visual acuity, corticosteroid dose and CFT were compared using Anova test. For patients treated with anti-TNF-α agents secondary to a relapse with DMARDs, the corticosteroid dose at the time of treatment failure was compared using paired *t*-test. Statistical analyses were performed using R Studio Version 1.0.153 and GraphPad Prism Version 8.1.2 and p values ≤ 0.05 were considered to be statistically significant.

3. Results

3.1. Patients' characteristics

Among 279 patients with non-infectious non-anterior uveitis, 73 patients were included. Two hundred and six patients were excluded: 181 with corticosteroids alone, 7 with interferon alpha2a, 2 with tocilizumab and 16 with incomplete data. Thirty-four patients were treated with anti-TNF-α agents (47%): 19 with adalimumab (40 mg every 2 weeks) and 15 with infliximab (5 mg/kg at weeks 0, 2, 6, and then every 4, 6 or 8 weeks). Thirty-nine patients were treated with DMARDs (53%): 15 with azathioprine, 14 with methotrexate and 10 with mycophenolate mofetil (1 g twice daily). Azathioprine doses were gradually increased from 100 to 150 mg/day, depending on the patient's weight (median of 118 mg/day). Similarly, methotrexate doses ranged from 7.5 mg/week to 20 mg/week (median of 13 mg/week), adjusted to the patient's weight. The follow-up period began at the initiation of the treatment (anti-TNF-α agents or DMARDs) until the primary outcome or, for patients who did not reach the primary outcome, the last visit. The median time (IQR) of follow-up was 9.5 months (4–22) in the anti-TNF-α group and 13 months (4–37) in the DMARD group.

The median age (IQR) at the initiation of treatment was 42.5 years old (32–61) in the anti-TNF-α group and 49 years old (34–61) in the DMARD group ($p = 0.47$) (Table 1). The main uveitis etiologies in the two groups were: idiopathic uveitis, i.e. 32% in the anti-TNF-α group and 28% in the DMARD group and birdshot chorioretinopathy, respectively 24% and 26%. The third etiology was Behçet's disease for patients treated with anti-TNF-α agents and sarcoidosis for patients treated with DMARDs. Most of the uveitis (90%) was bilateral. Seventeen patients (50%) treated with anti-TNF-α agents had posterior uveitis and 56% of the patients treated with DMARDs had pan-uveitis. There was no significant difference between the two groups, concerning general characteristics, uveitis etiology, or initial ophthalmologic characteristics (visual acuity, ocular inflammation, retinal vasculitis, cystoid macular edema). Patients treated with anti-TNF-α agents had a significantly longer uveitis course ($p = 0.05$), were exposed longer to corticosteroids ($p = 0.05$) and had more frequent relapses ($p = 0.01$). Finally, 68% of patients treated with anti-TNF-α agents had previously been treated with DMARDs ($p < 0.0001$).

3.2. Primary outcome

The primary outcome was observed in 19/34 patients (56%) in the anti-TNF-α group and in 23/39 patients (59%) in the DMARD group ($p = 0.82$) (Table 2). Treatment failure occurred in 14/19 patients (41%) in the anti-TNF-α group and 19/23 patients (49%) in the DMARD group ($p = 0.64$). Serious adverse events requiring treatment discontinuation occurred in 5/19 patients (14%) in the anti-TNF-α group and in 4/23 patients (10%) in the DMARD group ($p = 0.73$). The primary outcome was observed in patients with idiopathic uveitis (74%), birdshot chorioretinopathy (72%), sarcoidosis (58%) and Behçet's disease (20%) ($p = 0.02$). The median time to observe the primary outcome was 16 months for patients treated with anti-TNF-α agents and 21 months in the DMARD group ($p = 0.52$) (Fig. 1). In the anti-TNF-α group, rates of event-free survival were 70.4% at 6 months, 60.4% at 12 months, and 43.7% at 24 months. In the DMARD group, rates of event-free survival were 71.7% at 6 months, 60.3% at 12 months, and 46.5% at 24 months.

Table 1
Demographic and clinical characteristics of the 73 patients. R/LE = right/left eye.

	Anti-TNF-α	DMARDs	p
	34 (47)	39 (53)	
Median age (IQR)	42.5 (32–61)	49 (34–61)	0.47
Male sex	20 (59)	15 (38)	0.10
Median time of evolution (months) (IQR)	14.5 (8.3–66)	11 (4–28)	0.05
Uveitis etiology			
Idiopathic	11 (32)	11 (28)	0.80
Birdshot chorioretinopathy	8 (24)	10 (26)	0.99
Behçet's disease	7 (21)	3 (8)	0.17
Sarcoïdosis	3 (9)	9 (23)	0.12
Multifocal choroiditis	3 (9)	0	0.1
Vogt-Koyanagi-Harada	0	4 (10)	0.12
Others	2 (6)	2 (5)	0.99
Uveitis characteristics			
Bilateral	31 (91)	36 (92)	0.99
Localization			
intermediary	1 (3)	2 (5)	0.99
posterior	17 (50)	15 (39)	0.35
pan-uveitis	16 (47)	22 (56)	0.49
Median visual acuity (LogMAR) RE (IQR)	0.4 (0–0.50)	0.15 (0.10–0.45)	0.57
Median visual acuity (LogMAR) LE (IQR)	0.19 (0–0.50)	0.22 (0.10–0.50)	0.81
Anterior chamber cell (Tyndall ≥ 1+)	10 (30)	10 (27)	0.80
Vitreous haze grade (Nussenblatt ≥ 1+)	15 (45)	13 (36)	0.47
Granulomatous	2 (6)	4 (11)	0.68
Retinal vasculitis	11 (32)	14 (41)	0.62
Cystoid macular edema	18 (55)	23 (62)	0.63
Previous relapse (median, IQR)	1.5 (0–3)	0 (0–1)	0.01
Uveitis treatment			
Duration of corticosteroid treatment (months)	13 (5–63)	8 (3–26)	0.05

Table 2
Primary outcome and reasons for treatment failure in patients treated with anti- TNF-α or DMARDs.

	Anti-TNF-α	DMARDs	p
Primary outcome	19 (56)	23 (59)	0.82
Treatment failure	14 (41)	19 (49)	0.64
Serious adverse events	5 (14)	4 (10)	0.72
Reasons for treatment failure			
Worsening of Best Corrected Visual Acuity	6 (43)	6 (32)	0.48
Anterior chamber cell	2 (14)	3 (16)	0.99
Vitreous haze	3 (21)	5 (26)	0.99
Retinal vasculitis	2 (14)	5 (26)	0.67
Cystoid macular edema	9 (64)	10 (53)	0.74
Treatment failure after treatment decrease	2 (6)	1 (3)	0.6

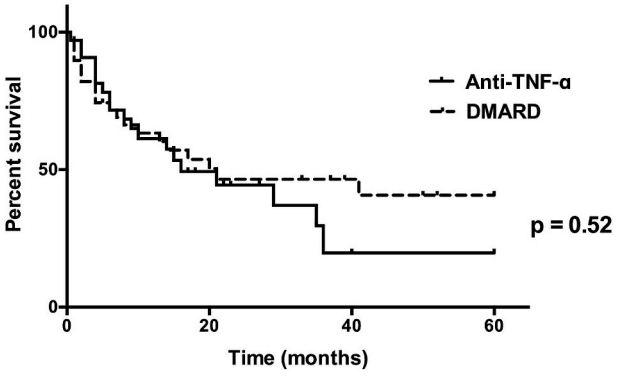

Fig. 1. Median time to observe the primary outcome in patients treated with anti-TNF-α agents (continuous line) or DMARDs (dashed line).

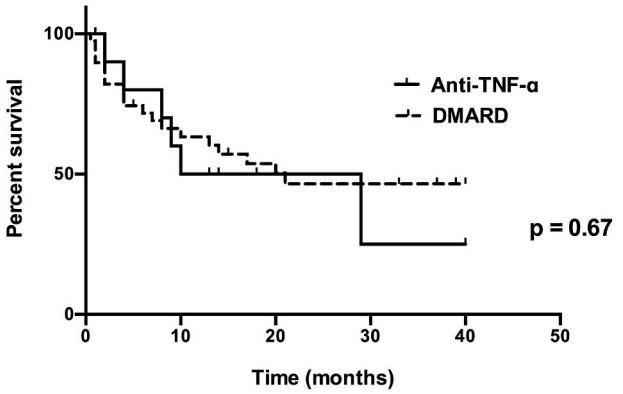

Fig. 2. Median time to observe the primary outcome in patients receiving first-line anti-TNF-α agents (naïve patients) (continuous line) or DMARDs (dashed line).

Anti-TNF-α agents were used as first-line therapy in three patients with Behçet's disease, in three patients with severe retinal vasculitis, in two patients with an initially high level of steroid dependency, in one patient with one functional eye, in one patient with concomitant rheumatic disease and in one patient who refused DMARD treatment. In a sub-group analysis, including patients previously treated with only corticosteroid, the median time to observe the primary outcome was 19.5 months in naïve patients of the anti-TNF-α group (n = 11) and 21 months with DMARDs (p = 0.67) (Fig. 2).

The median time to observe the primary outcome was 10 months with adalimumab, 29 months with infliximab, 15.5 months with methotrexate, 41 months with mycophenolate mofetil and not calculable with azathioprine (p = 0.74).

The primary ocular event leading to treatment failure was the increase or the development of cystoid macular edema, in both groups (9/14 patients (64%) in the anti-TNF-α group and 10/19 patients (53%) in the DMARD group, p = 0.74). There was no difference between the two groups regarding the reason for treatment failure (Table 2). Treatment failure management was treatment switch in seven patients in the anti-TNF-α group (50%) and in nine patients in the DMARD group (47%) (p = 0.47). Corticosteroid dose increase was performed in two patients in the anti-TNF-α group (13%) and in nine patients in the DMARD group (47%) (p = 0.07).

3.3. Secondary outcomes

There was an improvement of visual acuity, with no significant difference between the two groups (p = 0.50) during the first year of treatment. In the anti-TNF-α group, median (IQR) visual acuity was 0.4 LogMAR (0–0.50) in the right eye and 0.19 LogMAR (0–0.50) in the left eye at the time of treatment ini-tiation. At 12 months, visual acuity improved to 0.075 LogMAR (0–0.50) in the right eye and to 0.1 LogMAR (0.025–0.26) in the left eye. In the DMARD group, median (IQR) visual acuity was 0.15 LogMAR (0.10–0.45) in the right eye and 0.22 LogMAR (0.10–0.50) in the left eye at the time of treatment initiation. At 12 months, visual acuity improved to 0.05 LogMAR (0–0.15) in the right eye and to 0 LogMAR (0–0.22) in the left eye. During follow-up, improvement of initial cystoid macular edema occurred in 44% and 48% in the anti-TNF-α group and DMARD group, respectively, after one year of treatment (p = 0.99). Initial retinal vasculitis disappeared in 67% and 71% in the anti-TNF-α and DMARD groups respectively, after one year of treatment (p = 0.99).

At inclusion, 44% and 51% of patients had ocular quiescence in the anti-TNF-α and DMARD groups, respectively (p = 0.64). Anti-TNF-α agents allowed rapid control of intraocular inflammation i.e. ocular quiescence occurred in 92% in the anti-TNF α group and 57% in the DMARD group, after 6 months of treatment (p = 0.006). After 12 months, the difference became non-significant i.e. 72% in the anti-TNF-

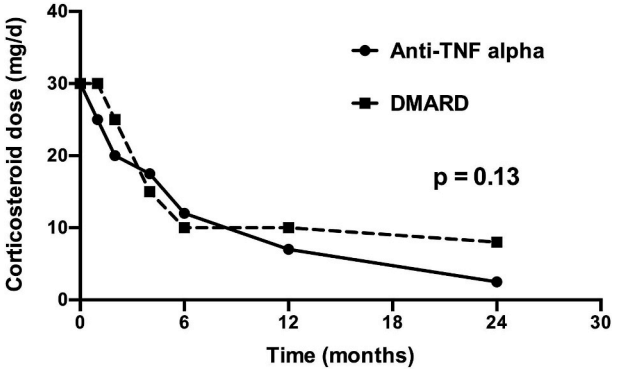

Fig. 3. Corticosteroid-sparing effect for patients treated with anti-TNF-α agents (continuous line) or DMARDs (dashed line).

α group and 59% in the DMARD group (p = 0.51).

The median corticosteroid dose at initiation of anti-TNF-α agents was 30 mg/day (20–49) and decreased to 2.5 mg/day (0–9) after 24 months (p < 0.0001). In the DMARD group, the median initial corticosteroid dose was 30 mg/day (20–46) and decreased to 8 mg/day (7–9) after 24 months (p < 0.0001). There was no significant difference in corticosteroid sparing effect between the two groups (p = 0.13) (Fig. 3). Corticosteroids were withdrawn in eight patients (24%) in the anti-TNF-α group versus five patients (13%) in the DMARD group (p = 0.36). Among patients in the anti-TNF-α agents group who presented treatment failure (n = 14), 9 patients had previously relapsed with DMARDs. The median corticosteroid dose at the time of anti-TNF-α failure was 12.5 mg/day (6–20). In the same patients, corticosteroid dose at the time of DMARD failure was 20 mg/day (12–30) (p = 0.06).

At the end of follow-up, the primary outcome was not observed in 16 patients in each group. Six patients in the anti-TNF-α group and five in the DMARD group stopped their treatment (p = 0.99). One patient in the anti-TNF-α group and three patients in the DMARD group relapsed after treatment discontinuation.

3.4. Safety

Eighteen patients (53%) treated with anti-TNF-α agents and 15 patients (38%) treated with DMARDs had at least one adverse event during follow-up (p = 0.36). Five patients with anti-TNF-α agents required treatment discontinuation, i.e. gastro-intestinal bleeding, severe bullous psoriasis, suicidal ideation, anaphylactic reaction with infliximab, and suicidal ideation with adalimumab. Four patients with DMARDs required treatment discontinuation, i.e. febrile diarrhea with azathioprine (two patients), acute pancreatitis with azathioprine and pneumocystis with methotrexate (Table 3).

Table 3
Adverse events in patients treated with anti-TNF-α agents or DMARDs.

	Anti-TNF-α	DMARDs	p
Any adverse event	18 (53)	15 (38)	0.36
Adverse events leading to treatment discontinuation	5 (15)	4 (10)	0.73
Serious infection	0	0	
Other infection	11 (32)	5 (13)	0.09
Tuberculosis	0	0	
Serious adverse events			
Gastroenteritis symptoms	4 (12)	6 (15)	
Elevation of the liver enzyme	1 (3)	2 (5)	
Cancer	1 (3)	2 (5)	
Depression	3 (9)	0	
Auto-immune reaction	2 (6)	0	
Allergic reactions	1 (3)	0	
Cytopenia	0	1 (3)	
Non-serious adverse events			
Headache	3 (9)	1 (3)	
Fatigue	0	2 (5)	
Hallucinations	1 (3)	0	

4. Discussion

In this single center retrospective study, we compared two current therapeutic strategies for the treatment of non-infectious non-anterior uveitis: anti-TNF-α agents and DMARDs. We have shown that the rate and the median time to observe the primary outcome were not statistically different between the two treatments. Moreover, there was no significant difference between treatment with anti-TNF-α agents or with DMARDs in improvement of visual acuity, reduction of cystoid macular edema and retinal vasculitis or in number of serious adverse events. However, anti-TNF-α agents appeared to be more effective in the early control of intraocular inflammation and corticosteroid tapering. In the anti-TNF-α group, uveitis was more severe because 68% of patients had previously relapsed with DMARDs and were therefore at greater risk of treatment failure.

Indications for immunosuppressive drugs i.e. DMARDs or anti-TNF-α agents were related to the etiology of uveitis and its severity, the initial level of steroid dependency and patients' medical history and background. The results of our cohort are consistent with the fact that many patients with non-infectious non-anterior uveitis do not need immunosuppressive drugs or biologics [7].

The event-free survival rate in our anti-TNF-α group was lower than that of Vallet et al. [15]: 90% at 6 months in their study versus 70.4%, 70% at 12 months versus 60.4% and 59% at 24 months versus 43.7% in our study. However, our definition of treatment failure was stricter because we included visual acuity, as previously used [12,13]. Furthermore, in our study, after 24 months of treatment, the primary outcome was observed in 56.3% of patients in the anti-TNF-α group and in 53.5% in the DMARD group, emphasizing the severity of uveitis and the high risk of treatment failure.

Interestingly, our subgroup analysis comparing first-line therapy did not show a significant difference in the rate and median time to observe the primary outcome. Patients treated with first-line anti-TNF-α agents (naïve patients) probably had more severe disease such as retinal vasculitis suggestive of Behçet's disease, which may explain the lack of difference between the two groups. However, in the large prospective VISUAL I study [12], adalimumab was not statistically more effective to prevent relapse than placebo in the subgroup of patients concurrently treated with conventional immunosuppressant therapy.

Anti-TNF-α agents efficacy in the control of ocular inflammation has already been demonstrated [12,16,17], leading the EULAR (European league against rheumatism) recommendations to propose anti-TNF-α agents, in cases of posterior involvement in Behçet's disease, as first-line therapy [18]. These recommendations in Behçet's disease were extrapolated, in our clinical practice, to treat cases of uveitis that appeared initially severe or in case of patient-specific criteria such as having only one functional eye. Our study has shown the superiority of anti-TNF-α agents over DMARDs in the early control of ocular inflammation. As a consequence, anti-TNF-α agents could be proposed as the first-line treatment strategy in cases of severe ocular inflammation with visual function impairment. However, anti-TNF-α agents do not appear to be effective for all patients. In the VISUAL III trial [19], a prospective study in which all the patients of VISUAL I and II studies (371 patients) were included, only 60% of patients with active uveitis were quiescent at the end of the study.

Anti-TNF-α [20] and DMARD [21] efficacy on corticosteroid sparing effect has already been described. Interestingly, after a previous relapse on DMARDs (n = 9), patients on anti-TNF-α agents had a lower corticosteroid dose at the time of treatment failure (p = 0.06). In the VISUAL II study [13], adalimumab improved the median time to treatment failure, compared to placebo, while corticosteroids were tapered off within 19 weeks after inclusion.

In the two groups, the first parameter which defined treatment failure was the appearance or persistence of cystoid macular edema. Interestingly, the evolution of pre-existing macular edema with adalimumab was not mentioned in VISUAL I [12] and II [13] trials. In our study, cystoid macular edema disappeared in 50% of the patients in both groups ($p = 0.99$), consistent with literature data [22–24]. Schaap-Fogler et al. [25] compared the efficacy of DMARDs and anti-TNF-α agents and found no significant difference after 12 months in the reduction of central macular thickness. This is a major focus for new therapies, such as tocilizumab, an anti-IL-6 receptor [26].

The safety profile was similar between the two groups, even though there was a trend for increased infections with anti-TNF-α agents ($p = 0.09$). Unexpectedly, we detected depressive syndromes leading to anti-TNF-α treatment discontinuation. Few depressive syndromes secondary to anti-TNF-α agents have been described, only case reports with confounding factors [27]. In the VISUAL I study, the onset of suicidal ideation also lead to treatment discontinuation [12]. We found fewer adverse events with DMARDs than in the literature, probably secondary to lower dosage [28].

Our study has some limitations. This is a single center retrospective study, which represents a potential indication bias. Due to study inclusion criteria, patients in the anti-TNF-α group had a significantly longer course of uveitis, relapsed more frequently and probably had more severe uveitis. We chose to use a composite primary outcome to evaluate both the efficacy of the treatment and its tolerance, thus enabling us to approach the “real-life” conditions of prescription. Moreover, among patients treated with adalimumab, only one patient received a loading dose, which may have contributed to the absence of significant difference between the two groups. Furthermore, we observed a lack of power due to our sample size.

The originality of this study is that we compare the efficacy of anti-TNF-α agents versus DMARDs in the treatment of uveitis. Nonetheless, prospective studies comparing first-line therapy with DMARDs or anti-TNF-α agents are needed.

In conclusion, DMARDs could still be used as first-line therapy for non-infectious non-anterior uveitis after corticosteroid therapy. However, anti-TNF-α agents could be proposed as an alternative in cases of severe ocular inflammation or initial high level of steroid dependency. Despite these new treatments, uveitis prognosis remains severe.

CRediT authorship contribution statement

Mathilde Leclercq: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Vincent Langlois:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft. **Nicolas Girszyn:** Conceptualization, Data curation, Investigation, Writing - original draft. **Maëlle Le Besnerais:** Data curation, Investigation, Writing - review & editing. **Ygal Benhamou:** Formal analysis, Validation, Writing - review & editing. **Hervé Levesque:** Methodology, Validation, Writing - review & editing. **Marc Muraine:** Supervision, Validation, Writing - review & editing. **Julie Gueudry:** Conceptualization, Methodology, Supervision, Validation, Writing - review & editing.

Declaration of competing interest

None.

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