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Efficacy of Anti-TNF-α Therapy for the Treatment of Non-infectious Uveitis: A Retrospective Study of 21 Patients

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ABSTRACT

Purpose: To assess the efficacy of anti-TNF alpha (TNF-α) therapy in patients with non-infectious uveitis.

Methods: This was a monocentric observational study of 21 patients with non-infectious uveitis treated with anti-TNF-alpha. The primary endpoint was the control of ocular inflammation. The secondary endpoints included the study of macular thickness and visual acuity, changes in other treatments, and adverse effects.

Results: The etiologies of uveitis were Behçet disease (33.3%), birdshot (14.3%), sarcoidosis (9.5%), and idiopathic uveitis (42.9%). Ocular inflammation was controlled at 3 months for 80.9% of patients, at 6 months for 94.7%, at 12 months for 83.3%, and at >12 months for 86.7%. Central macular thickness improved from 452 µm at baseline to 307.5 µm at 12 months (p = 0.002). Visual acuity also improved from 0.51(logMAR) before treatment to 0.24 at 12 months. The mean daily dose of prednisone decreased from 19.7 mg before treatment to 5.2 mg at 12 months (p < 0.001). A total of 9.5% of patients experienced serious side-effects.

Conclusions: Our study confirms the efficacy of anti-TNF for the control of short-term and long-term ocular inflammation, with high rates of complete clinical remission.

Keywords: Adalimumab, anti-TNF-α, refractory uveitis

Non-infectious uveitis may represent 10–15% of all blindness in developed countries, and are the fifth leading cause of blindness in middle-aged patients, predominantly between 20 and 50 years of age.¹ This is a difficult-to-treat disease due to the complexity of its physiopathology. In order to control the ocular inflammation, long-term treatments are often necessary. Corticosteroids (local and systemic) are used in first-line treatment but they are associated with many side-effects. Immunosuppressive drugs, including methotrexate, azathioprine, and mycophenolate mofetil are used in second-line treatment.²

The development of biotherapy, in particular against tumor necrosis factor alpha (TNF-α), led to new therapeutic options, especially when corticosteroids and immunosuppressive drugs are poorly tolerated or are not effective to control the ocular inflammation. TNF-α is a pro-inflammatory cytokine, discovered in 1975,³ which plays a critical role in the physiopathology of uveitis. It is mainly produced by CD4+ T helper cells, macrophages, polymorphonuclear neutrophils, and by endothelial cells. It stimulates the proliferation of inflammatory cells (including macrophages), the expression of adhesion molecules on endothelial cells, and also induces the secretion of other proinflammatory cytokines (IL-1, IL-6) and nitric oxide by macrophages. Elevated levels of TNF-α have been found in animal models of uveitis,⁴ such as experimental autoimmune uveitis (EAU), and in patients with uveitis.⁵ In addition, neutralizing TNF-α in EAU was shown to suppress macrophage activation and thus the production of nitric oxide, thereby inducing the reduction of retinal lesions.⁶
In 2004, Murphy et al. were the first to publish the efficacy of anti-TNF-α in the treatment of uveitis. Since then, its use has been constantly increasing. Thanks to the different published studies, adalimumab received Food and Drug Administration approval in June 2016, to treat adults with non-infectious intermediate, posterior, and panuveitis.

In this study, we report our experience with the use of anti-TNF-α (infliximab and adalimumab) in patients with non-infectious recalcitrant uveitis, with an analysis of changes in associated treatments, safety, and side-effects.

PATIENTS AND METHODS

Study Population

In this monocentric observational retrospective study from January 1, 2010 to October 1, 2015, all patients (age ≥18 years) with non-infectious uveitis treated with anti-TNF-α agents and followed in the departments of ophthalmology and internal medicine of the University Hospital of Bordeaux, France, were included. All patients had an active uncontrolled ocular inflammation at the time of the first anti-TNF-α injection, with at least one immunosuppressive treatment failure for most patients. Patients must not have been followed in other clinical centers.

Efficacy Objectives

The primary objective was the control of ocular inflammation defined by a lack of anterior chamber and vitreous cells, a reduction of macular edema, and a lack of vasculitis or papilledema confirmed by fluorescein angiography (HRA 2, Heidelberg Engineering, Heidelberg, Germany). The secondary objectives included the full analysis of the evolution of the mean macular thickness (MMT) in the central 1 mm area, measured using optical coherence tomography (OCT) (Cirrus, Carl Zeiss Meditec, Dublin, CA), the improvement in visual acuity, and the changes in other systemic or local treatments, including corticosteroids withdrawal.

Data Collection

Evaluations were performed at baseline (M0), and after 3 months (M3), 6 months (M6), and 12 months (M12) following the anti-TNF-α treatment initiation. The long-term effect of the anti-TNF-α treatment was also analyzed beyond 12 months (M>12) but only for the primary efficacy objective. The following information was collected for each patient: demographic data (age, sex); presumed or proven etiology of uveitis; systemic and ocular medical history; type of anti-TNF-α used (infliximab or adalimumab); date of initiation; time between injections; age at the first injection; and duration of follow-up. Ophthalmic examination of each eye included: the anatomic classification of the uveitis (according to the Standardization of Uveitis Nomenclature Working Group); the MMT in the central 1 mm area using OCT at M0, M3, M6, and M12; peripapillary retinal nerve fiber layer thickness using OCT at M0, M3, M6, and M12; best-corrected visual acuity (BCVA) assessed using the logMAR and the Snellen charts at M0, M3, M6, and M12; the presence (or not) of a recurrence of the ocular inflammation during the anti-TNF-α therapy, the date of recurrence, the type of recurrence, and the treatment prescribed. Regarding the therapy, the following information was collected: previous and concomitant systemic treatments (corticosteroids and immunosuppressive drugs); previous and concomitant local corticosteroids (topical, subconjunctival, subtenon, or intravitreal injection); adverse events and safety.

Administration of Anti-TNF-α

An examination before the initiation of the anti-TNF-α therapy was systematically performed. This included physical examination, laboratory test evaluation (complete blood count, serum protein electrophoresis, transaminases, hepatitis serology, antinuclear antibodies, in vitro QuantiFERON-TB-Gold® or T-Spot-TB®), chest radiograph, and a control of valid vaccination certificates. Infliximab was administered as one intravenous injection of 5 mg/kg at 0, 2, and 6 weeks, and then every 6 weeks. Adalimumab was administered as one subcutaneous injection of 40 mg every 2 weeks. Injections could be progressively spaced in case of controlled inflammation. A biologic control, including a complete blood cell count, a C-reactive protein (CRP) and transaminases, was performed before each administration of infliximab and every 3 months for adalimumab, in order to eliminate any infectious process or hepatic toxicity.

Statistical Analysis

Statistical analysis was performed using the EXCEL Software. Qualitative variables were described using frequency and percentages and quantitative variables using means, standard deviations (SD), and range (minimal and maximal values). Continuous variables were analyzed with the Wilcoxon signed rank test (macular thickness and mean dose of systemic corticosteroids). A p value of <0.05 was considered statistically significant. Data were summarized both in tables and histograms.
RESULTS

A total of 33 patients were first selected; 12 of them were excluded: two patients because the anti-TNF-α therapy was not initiated for an uncontrolled ocular inflammation but for the treatment of a systemic disease and 10 patients because they were not completely followed-up at the ophthalmology or internal medicine department of the University of Bordeaux. Thus, 21 patients were analyzed (33 eyes): 10 men (47.6% of patients) and 11 women (52.4% of patients). Mean age at first injection of anti-TNF-α was 51.4 ± 15.5 years (range: 22–81 years). The mean duration of follow-up was 31.7 ± 13.1 months (range: 13–67 months). During the 12-month study period, anti-TNF-α therapy was discontinued in some patients. Thus, 21 patients were analyzed at M3; 19 patients at M6 (treatment discontinuation in two patients due to adverse events); 18 patients at M12 (treatment switch in one patient); and 15 patients at M>12 (treatment stop following quiescent disease in two patients and for adverse events in one patient). Different subgroups were defined according to the etiology (Table 1): Behçet disease (n = 7, 33.3% of patients), birdshot disease (n = 3, 14.3% of patients), sarcoidosis (n = 2 patients, 9.5%), and idiopathic uveitis (n = 9, 42.9%).

Initially, 61.9% of patients were treated with infliximab (n = 13), and 38.1% with adalimumab (n = 8). Before the initiation of anti-TNF-α therapy, 95.2% (n = 20) of patients had been previously treated with one or several immunosuppressive treatments, with insufficient efficacy to control the ocular inflammation. One patient was not treated with an immunosuppressive agent before anti-TNF-α therapy because he had an initial severe bilateral idiopathic panuveitis; 90% (n = 18) of them had a corticosteroid therapy (prednisone) (Table 1). In addition to systemic treatment, 80.9% of patients (n = 17) were treated with a local ocular treatment.

Switch of anti-TNF-α occurred in three patients: one patient from adalimumab to infliximab after 9 months of treatment due to uncontrolled ocular inflammation; one patient from adalimumab to infliximab after 13 months of treatment due to uncontrolled systemic disease; and one patient with a controlled ocular inflammation from infliximab to adalimumab after 12 months of treatment due to practical reasons (to avoid repeated hospitalization).

Control of Ocular Inflammation

At M3, ocular inflammation was controlled in 80.9% of patients (n = 17), including 100% (n = 13) of patients treated with infliximab and 50% (n = 4) treated with adalimumab (Figure 1). Non-responders or patients with recurrence of ocular inflammation within the first 3 months were all treated with adalimumab. According to the etiology, the rate of controlled patients was 100% in patients with Behçet disease (n = 7); 100% in patients with birdshot disease (n = 3); 100% in patients with sarcoidosis (n = 2); and 55.5% in patients with idiopathic uveitis or other etiology (n = 5) (Figure 2). Thus, non-responders within 3 months of anti-TNF-α therapy were patients with idiopathic uveitis.

At M6, ocular inflammation was controlled in 94.7% of patients (n = 18), including 100% (n = 12) of patients

### TABLE 1. Clinical data of enrolled patients.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Etiology</th>
<th>Anatomic classification</th>
<th>Uni/bilateral</th>
<th>Previous oral treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Behçet</td>
<td>Panuveitis</td>
<td>Unilateral</td>
<td>Prednisone, AZA</td>
</tr>
<tr>
<td>7</td>
<td>Behçet</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>Prednisone, AZA</td>
</tr>
<tr>
<td>10</td>
<td>Behçet</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>Prednisone, AZA</td>
</tr>
<tr>
<td>11</td>
<td>Behçet</td>
<td>Panuveitis</td>
<td>Unilateral</td>
<td>Prednisone</td>
</tr>
<tr>
<td>14</td>
<td>Behçet</td>
<td>Intermediate uveitis</td>
<td>Unilateral</td>
<td>Prednisone, AZA</td>
</tr>
<tr>
<td>18</td>
<td>Behçet</td>
<td>Acute anterior uveitis</td>
<td>Unilateral</td>
<td>NSAID, MTX</td>
</tr>
<tr>
<td>20</td>
<td>Behçet</td>
<td>Posterior uveitis</td>
<td>Unilateral</td>
<td>Prednisone</td>
</tr>
<tr>
<td>1</td>
<td>Birdshot</td>
<td>Posterior uveitis</td>
<td>Unilateral</td>
<td>CSA, prednisone, MMF</td>
</tr>
<tr>
<td>12</td>
<td>Birdshot</td>
<td>Posterior uveitis</td>
<td>Bilateral</td>
<td>Prednisone, MMF</td>
</tr>
<tr>
<td>13</td>
<td>Birdshot</td>
<td>Posterior uveitis</td>
<td>Bilateral</td>
<td>Prednisone, MMF</td>
</tr>
<tr>
<td>4</td>
<td>Sarcoidosis</td>
<td>Neurosarcoidosis</td>
<td>Bilateral</td>
<td>Prednisone</td>
</tr>
<tr>
<td>8</td>
<td>Sarcoidosis</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>Prednisone, MTX, AZA</td>
</tr>
<tr>
<td>2</td>
<td>Idiopathic</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>Prednisone, MTX</td>
</tr>
<tr>
<td>3</td>
<td>Idiopathic</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>Prednisone, AZA, MMF, immunoglobulin</td>
</tr>
<tr>
<td>5</td>
<td>Idiopathic</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>MTX</td>
</tr>
<tr>
<td>9</td>
<td>Idiopathic</td>
<td>Posterior uveitis</td>
<td>Bilateral</td>
<td>Prednisone, AZA, MTX</td>
</tr>
<tr>
<td>15</td>
<td>Idiopathic</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>Prednisone, AZA</td>
</tr>
<tr>
<td>16</td>
<td>Idiopathic</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>Prednisone, MTX</td>
</tr>
<tr>
<td>19</td>
<td>Idiopathic</td>
<td>Posterior uveitis</td>
<td>Unilateral</td>
<td>Prednisone, MTX</td>
</tr>
<tr>
<td>21</td>
<td>Idiopathic</td>
<td>Panuveitis</td>
<td>Bilateral</td>
<td>None</td>
</tr>
<tr>
<td>17</td>
<td>Sympathetic ophthalmia</td>
<td>Panuveitis</td>
<td>Unilateral</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>

AZA, azathioprine; CSA, cyclosporin A; MMF, mycophenolate mofetil; NSAID, non-steroidal anti-inflammatory drugs.
Changes in Macular Thickness and Visual Acuity

A progressive decrease in MMT was observed after the initiation of the anti-TNF-α therapy from 452 µm at M0 to 334.6 µm at M3, 337.1 µm at M6, and 307.5 µm at M12 (p = 0.002), i.e. a 32% reduction (Table 2).

Furthermore, a progressive increase in the mean visual acuity (logMAR) was observed after initiation of the anti-TNF-α therapy from 0.51 at M0 to 0.33 at M3, 0.28 at M6, and 0.24 at M12 (Table 2). The mean BCVA was improved from 35.3% at M3 to 52.9% at M12. Visual acuity was also improved by 2 lines in 48.1% of patients at M3 and 78.3% (i.e. >3/4 patients) at M12. Overall, 72.7% of studied eyes (n = 24/33) had a BCVA ≤20/50 before the anti-TNF-α therapy versus only 29.6% (n = 8/27) after 12 months of therapy.

Changes in Systemic and Local Therapies

For almost all patients (87.5%, n = 14/16), the systemic corticosteroid therapy was reduced or completely discontinued with anti-TNF-α therapy, while at previous attempts, most patients presented a relapse, a corticosteroid dependence or resistance. A total withdrawal of the corticosteroid therapy was obtained in 37.5% of patients (n = 6/16), two patients still received a small dosage during anti-TNF-α therapy and none had to increase the corticosteroid therapy. The average daily dose of prednisone was decreased from 19.7 mg at M0 to 5.2 mg at M12 (p = 0.001) (Table 3). Regarding other immunosuppressive treatments, only 9.5% of patients (n = 2) had methotrexate associated with the anti-TNF-α therapy at M12 (Table 3). Anti-TNF-α therapy allowed the withdrawal of other immunosuppressive treatments, while keeping a controlled ocular inflammation and systemic disease activity. Finally, 76.5% of patients (n = 13/17) benefited from a total withdrawal of local corticosteroids with anti-TNF-α (Table 3). Four patients still required a local treatment, including two patients for an uncontrolled acute anterior uveitis and two patients to treat a persistent macular edema.

Side-effects and Safety of the Anti-TNF-α Therapy

A total of 9.5% of patients (n = 2) experienced serious adverse events leading to treatment discontinuation: one patient with multiple sclerosis attributed to treatment (adalimumab), which occurred after 3 months of anti-TNF-α therapy, and one patient with severe infectious episodes with infliximab (Streptococcus necrotizing fasciitis of the right arm following the second injection, and dermo-hypodermitis of the left arm and the forearm due to Mycobacterium marinum after 5 months of treatment). In addition, 19% of patients treated with infliximab and 85.7% (n = 6) treated with adalimumab (Figure 1). According to the etiology, the rate of controlled patients was 100% in patients with Behçet disease (n = 7); 100% in patients with birdshot disease (n = 2); 100% in patients with sarcoidosis (n = 2); and 87.5% in patients with idiopathic uveitis or other etiology (n = 7) (Figure 2).

At M12, ocular inflammation was controlled in 83.3% of patients (n = 15), including 91.6% (n = 11) of patients treated with infliximab and 66.7% (n = 4) treated with adalimumab (Figure 1). According to the etiology, the rate of controlled patients was 85.7% in patients with Behçet disease (n = 6); 100% in patients with birdshot disease (n = 2); 50% in patients with sarcoidosis (n = 1); and 87.5% in patients with idiopathic uveitis or other etiology (n = 6) (Figure 2).

At M>12, ocular inflammation was controlled in 86.7% of patients (n = 13), including 90% (n = 9) of patients treated with infliximab and 80% (n = 4) treated with adalimumab (Figure 1). According to the etiology, the rate of controlled patients was 75% in patients with Behçet disease (n = 3); 100% in patients with birdshot disease (n = 2); 50% in patients with sarcoidosis (n = 1); and 100% in patients with idiopathic uveitis or other etiology (n = 7) (Figure 2).
TABLE 2. Macular thickness and visual acuity at each evaluation.

<table>
<thead>
<tr>
<th></th>
<th>M0</th>
<th>M3</th>
<th>M6</th>
<th>M12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean macular thickness (MMT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes (n)</td>
<td>20</td>
<td>20</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>MMT (μm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>452.0 ± 132.4</td>
<td>334.6 ± 66.0</td>
<td>337.1 ± 82.6</td>
<td>307.5 ± 51.9</td>
</tr>
<tr>
<td>Range</td>
<td>246–948</td>
<td>243–526</td>
<td>243–573</td>
<td>203–452</td>
</tr>
<tr>
<td>% change from pre-treatment</td>
<td>–</td>
<td>–26.0</td>
<td>–25.4</td>
<td>–32.0</td>
</tr>
<tr>
<td>p value between baseline and each evaluation</td>
<td>–</td>
<td>0.004</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Best-corrected visual acuity (BVCA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes (n)</td>
<td>33</td>
<td>33</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>BVCA (logMAR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.51 ± 0.38</td>
<td>0.33 ± 0.32</td>
<td>0.28 ± 0.26</td>
<td>0.24 ± 0.28</td>
</tr>
<tr>
<td>Range</td>
<td>0–2</td>
<td>0–2</td>
<td>0–2</td>
<td>0–2</td>
</tr>
<tr>
<td>% change from pre-treatment</td>
<td>–</td>
<td>35.3</td>
<td>45.1</td>
<td>52.9</td>
</tr>
<tr>
<td>% of patients with at least 2 lines (Snellen) improvement</td>
<td>–</td>
<td>48.1</td>
<td>56.0</td>
<td>78.3</td>
</tr>
</tbody>
</table>

SD, standard deviation.

TABLE 3. Treatment regimens at baseline and after 12 months of anti-TNF-α therapy.

<table>
<thead>
<tr>
<th></th>
<th>M0 (%)</th>
<th>M12 (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of prednisone (mg/day)</td>
<td>19.7</td>
<td>5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>16 76.2</td>
<td>10 47.6</td>
<td></td>
</tr>
<tr>
<td>Local corticosteroids (TOP, SC, ST, IVT)</td>
<td>17 80.9</td>
<td>4 19.0</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant (AZA, MMF, MTX, immunoglobulin)</td>
<td>16 76.2</td>
<td>2 9.5</td>
<td></td>
</tr>
</tbody>
</table>

AZA, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; TOP, topical; SC, subconjunctival; ST, subtenon; IVT, intravitreal.

(n = 4) experienced non-serious adverse events: one patient with hepatic cytolysis after 4 months of treatment, not self-limiting, and three patients (all under infliximab) with pseudofolliculitis on the back, which did not lead to treatment discontinuation.

One patient complained of pain at the injection site with adalimumab. Of note, in this study one pregnant patient with a severe uveal inflammation received the anti-TNF-α therapy without any side-effect during gestation or for the newborn.

**DISCUSSION**

In this study, the anti-TNF-α therapy led to an effective and sustained control of the uveal inflammation with a response rate of 80.9% at M3, increasing to a maximum of 94.7% at M6, which then seemed to stabilize with 83.3% and 86.7% at M12 and M>12, respectively. These rates are even more satisfactory as patients included in this study had previously an uncontrolled uveal inflammation, despite the use of different therapies. Using infliximab, results have been remarkable, with 100% of patients presenting a controlled inflammation at M3 and M6, 91.6% at M12, and 90% at M>12. In published studies, the initial efficacy of the anti-TNF-α was variable, ranging from 55.6% of responders to 100% at M3, as in our study. 

Consistently with other published studies, our work showed a very good efficacy of long-term therapy with infliximab at ≥M12. At M3 with adalimumab, only 50% of patients had a controlled ocular inflammation, with a marked improvement at ≥M6. A recent study assessed adalimumab efficacy in patients with active non-infectious uveitis, despite the use of corticosteroid therapy, with a 80 mg loading dose, 40 mg at week 1, followed by 40 mg every other week. This loading dose and dose regimen could be a solution for a quicker and stronger efficacy of adalimumab. Large cohort studies performed by Diaz-Llopis et al. in 2012 and Dobner et al. in 2013 reported the efficacy of adalimumab in the treatment refractory non-infectious uveitis. Very recently, a large retrospective multicenter study compared the efficacy of infliximab and adalimumab for the treatment of refractory non-infectious uveitis; anti-TNF treatment was highly effective and infliximab and adalimumab appeared to be equivalent in terms of efficacy in this study.

The analysis of the ocular inflammation control according to uveitis etiology in our study showed a higher response rate in patients with Behçet disease or birdshot disease. Previous studies performed to assess the efficacy of anti-TNF-α therapy in patients with Behçet disease led an expert group of the Executive Committee of the American Uveitis Society (Levy-Clarke et al.) in 2014 to place infliximab and adalimumab in second-line therapy after corticosteroids for the treatment of uveal illness (with infliximab in first-line). In birdshot disease, the efficacy of anti-TNF-α therapy has been studied in only a few papers. Regarding sarcoidosis, results in our
study were difficult to interpret because only two patients were involved. Many case reports and a recent study in 17 patients confirmed the efficacy of anti-TNF-α in the treatment of refractory uveitis associated with sarcoidosis. For idiopathic uveitis, the control of ocular inflammation in our study seemed slower compared with other etiologies. However, very good outcomes were obtained from M6. Similar results were reported by Lindstedt et al. in 2005. To date, no study was performed to specifically assess the efficacy of anti-TNF-α therapy in idiopathic uveitis. In 2014, the expert group of the Executive Committee of the American Uveitis Society (Levy-Clarke et al.) recommended the use of anti-TNF-α in birdshot disease, sarcoidosis-associated uveitis, and idiopathic uveitis in a third-line therapy, in case of failure or dependence to corticosteroids and if the response to immunosuppressive drugs was insufficient.

In our study, the anti-TNF-α therapy was effective on the macular edema with a statistically significant reduction of MMT at M3, M6, and M12. We observed a 26% reduction in MMT at M6 and 32% at M12. This is consistent with the role of TNF-α in the regulation andocular elevation of VEGF, inducing the development of macular edema and choroidal neovascularization. The efficacy of anti-TNF-α therapy on macular edema has been previously reported in several studies. It should be noted that the MMT reduction in our study was for the vast majority of patients exclusively due to the anti-TNF-α therapy. Indeed, among 11 patients in whom subconjunctival, subtenon, or intravitreous injections of corticosteroids was previously used to treat the macular edema, only two patients still required such injections with anti-TNF-α therapy.

In parallel, there was a clear improvement in BCVA (by 35.3% at M3, 45.1% at M6 and 52.9% at M12). This is a very important result for patients, since improved visual acuity helps to achieve a better quality of life.

Besides the control of ocular inflammation, withdrawal of systemic corticosteroids is another critical need, because even though a control of the ocular inflammation can be obtained with low doses of prednisone, adverse side-effects persist in the long term. In our study, corticosteroid sparing with anti-TNF-α therapy was obtained in 87.5% of patients, and a complete withdrawal was obtained in 37.5%. A statistically significant reduction in prednisone daily dose from 19.7 mg to 5.2 mg at M12 (p < 0.001) was observed. Local corticosteroid sparing is another essential need in order to avoid the risk of ocular hypertension and also of cataract in middle-aged patients. In our study, 76.5% of patients did not need local corticosteroids with anti-TNF-α therapy, which can be considered as a very good outcome. In 2012, Martel et al. reported the success of corticosteroid sparing in the control of chronic uveitis treated with anti-TNF-α therapy.

In our work, we chose not to associate an immunosuppressive drug in association with the anti-TNF-α (only 2/21 patients received methotrexate when treated with anti-TNF-α). Nevertheless, some studies performed in rheumatoid arthritis or in Crohn disease showed interesting results when an immunosuppressive drug was associated with the anti-TNF-α therapy: first because both treatments may have a synergistic effect, and second to prevent the formation of monoclonal autoantibodies, known to decrease the anti-TNF-α efficacy. However, no clinical studies have yet been performed to compare these two therapeutic options (anti-TNF-α alone versus anti-TNF-α associated with an immunosuppressive drug) in the treatment of non-infectious uveitis.

In our study, anti-TNF-α therapy was switched in three patients and in only one case because of a lack of ocular inflammation control (adalimumab switched to infliximab). Unfortunately, this switch was not effective. But several studies suggest that infliximab treatment failure is not associated to the resistance to adalimumab and vice versa. This is largely explained by the development of monoclonal autoantibodies. Even though this is uncommon in ophthalmology, switching to another anti-TNF-α is commonly used in rheumatology and in gastroenterology. Dhingra et al. reported a case series of seven patients with non-infectious uveitis, which responded favorably to anti-TNF-α switch, including three cases with two successive switches.

Anti-TNF-α may potentially induce severe side-effects, including viral and bacterial infections, severe anaphylactic reactions, demyelinating neurologic disorders, and the development of tumor (especially lymphoma). In our study, 9.5% of patients (n = 2) experienced such severe adverse events leading to treatment discontinuation. Overall, the anti-TNF-α therapy was stopped in 14.3% of patients (n = 3), which is a good rate when compared with other studies (19.3% of treatment discontinuation in the study performed by Kruh et al. and 19.4% in the study performed by Suhler et al. and 42, 43). One of our patients experienced atypical multiple sclerosis, which was related to infliximab. Anti-TNF-α therapy is not indicated in the case of personal or familial history of demyelinating pathology (which was not the case of our patient). Chen and Gordon recommend to perform a brain magnetic resonance imaging (MRI) in patients initially presenting with pars planitis ocular inflammation, 15% of them being susceptible to develop multiple sclerosis.

In our study, the anti-TNF-α therapy was stopped in two patients, following a quiescence of the disease, both ocular and systemic. For one patient, the ocular status was still quiescent after 40 months of anti-TNF-α therapy and 13 months of discontinuation. For the other patient, the anti-TNF-α therapy had been initiated for 27 months, discontinued for 13 months, and then resumed due to an ocular and systemic inflammatory relapse. Given the risk of side-effects and the treatment cost, it is recommended to consider anti-TNF-α withdrawal for patients completely controlled in terms of ocular and
systemic disease after 2 years of corticosteroid sparing, first by spacing the anti-TNF-α injections for at least 4 months before discontinuation. Switching to another immunosuppressive drug after discontinuation of the anti-TNF-α is still debated.

The main limitations of our study are the small number of patients and its retrospective design, leading to potential information biases. Some data were missing and, for example, the time to anti-TNF-α efficacy could not be accurately studied. Side-effects and anti-TNF-α safety have probably been underestimated, since only the most severe side-effects were reported in the patients’ files; mild side-effects, such as fatigue were not recorded.

This study provides evidence for the efficacy of anti-TNF-α to control ocular inflammation regardless of the non-infectious uveitis etiology and in particular when the uveitis is refractory to other therapy, including corticosteroids and immunosuppressive drugs. This efficacy was maintained in the long term. In the future, it would be interesting to specifically study the efficacy of anti-TNF-α therapy in a large cohort of patients with idiopathic uveitis, for which there are currently no available data in the literature.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES


