Efficacy of anti-tumour necrosis factor-α monoclonal antibodies in patients with non-infectious anterior uveitis

C. Fabiani[1,2], A. Vitale[3], D. Rigante[4], G. Emmi[5], G. Lopalco[6], J. Sota[3], L. Vannozzi[7], S. Guerriero[8], A. Bitossi[7], I. Orlando[3], R. Franceschini[2], B. Frediani[3], M. Galeazzi[3], F. Iannone[6], G.M. Tosi[2], L. Cantarini[3]

Claudia Fabiani, Antonio Vitale, Donato Rigante, Giacomo Emmi, Giuseppe Lopalco, Jurgen Sota, Lorenzo Vannozzi, Silvana Guerriero, Alice Bitossi, Ida Orlando, Rossella Franceschini, Bruno Frediani, Mauro Galeazzi, Florenzo Iannone, Gian Marco Tosi, Luca Cantarini

Please address correspondence to:
Luca Cantarini, MD, PhD,
Department of Medical Sciences,
Surgery and Neurosciences,
University of Siena,
Rheumatology Unit,
Policlinico "Le Scotte",
viale Bracci 1, 53100 Siena, Italy.
E-mail: cantariniluca@hotmail.com
or
Claudia Fabiani, MD, PhD,
Department of Ophthalmology,
Humanitas Clinical and Research Centre,
via Manzoni 56, 20089 Rozzano (MI), Italy.
E-mail: claudia.fabiani@gmail.com

For the affiliations, see page 304.

ABSTRACT

Objective. *To assess the efficacy of monoclonal anti-tumour necrosis factor (TNF)-α agents in patients with anterior uveitis (AU) in terms of decrease of recurrences, variation of visual acuity and steroid sparing effect and to identify any demographic, clinical or therapeutic variables associated with a sustained response to monoclonal TNF-α inhibitors.*

Methods. *Data from patients suffering from AU treated with adalimumab, infliximab, golimumab or certolizumab pegol were retrospectively collected and statistically analysed.*

Results. *Sixty-nine patients (22 males, 47 females), corresponding to 101 eyes, were enrolled. The mean follow-up period was 29.25±23.51 months. The rate of ocular flares decreased from 42.03 events/100 patients/year recorded during the 12 months preceding the start of TNF-α inhibitors to 2.9 flares/100 patients/year after the start of treatment (p<0.0001). The overall decrease in ocular flares was 93.1%. No statistically significant changes were identified in the best corrected visual acuity during the follow-up period (p>0.99). The number of patients treated with corticosteroids at baseline was significantly higher compared with that referred to the 12-month evaluation (p<0.001) and to the last follow-up visit (p=0.006). Concomitant treatment with conventional disease-modifying anti-rheumatic drugs (cDMARDs) represented the sole clinical, demographic or therapeutic variable associated with long-term treatment duration (p=0.045, R^2=0.87).*

Conclusion. *Monoclonal TNF-α inhibitors induce a remarkable decrease in the recurrence of AU during a long-term follow-up period and lead to a significant steroid sparing effect along with stabilisation of visual acuity. Concomitant treatment with cDMARDs represented the sole variable associated with treatment duration in the long-term.*

Introduction

Anterior uveitis (AU) is characterised by intraocular inflammation that primarily involves the anterior chamber of the eyeball: it is the most common type of uveitis starting more frequently from a non-infectious basis, with half of the cases being idiopathic. Non-infectious AU may occur as an isolated eye disease or may be associated with a systemic disorder. Most common diseases associated with non-infectious AU are seronegative HLA-B27-associated arthropathies, juvenile idiopathic arthritis (JIA) and Behçet's syndrome (BS) (1, 2).

While AU has often a benign course, it may sometimes induce sight-threatening complications, including extensive posterior synechiae, cataract, macular edema and glaucoma as a consequence of relapsing and persistent inflammation and/or long-term use of topical and systemic corticosteroids. By this reason AU may significantly affect patients' overall quality of life (3).

Consequently, a prompt and effective treatment is required to avoid irreversible sequelae and/or permanent visual loss. While conventional treatment is primarily based on cycloplegics along with short-term use of topical and systemic corticosteroids, accumulating evidences support an early introduction of conventional disease-modifying anti-rheumatic drugs (cDMARDs) as adjunctive steroid-sparing agents in patients with recalcitrant and refractory non-infectious AU (1, 4-7). More recently, the use of monoclonal inhibitors of tumour necrosis factor (TNF)-α has also been proposed as a further effective therapeutic choice. In particular, expert panel recommendations on the use of TNF-α blockers in patients with non-infectious uveitis suggest the use of the monoclonal TNF-α inhibitors infliximab (IFX) and adalimumab (ADA) for patients with SpA and relapsing AU or in patients with spondyloarthritis (SpA) and severe or disabling uveitis requiring additional therapies (5). Moreover, the efficacy of monoclonal TNF-α blockers has also been shown for patients with AU associated with other rheumatologic conditions different from SpA (8-10). In addition, recent clinical experience has also suggested a promising role of golimumab (GOL) and certolizumab pegol (CZP), two other monoclonal anti-TNF-α agents, for the treatment of uveitis (11, 12). In this context, goal of

the present study was to assess the role of monoclonal TNF-α inhibitors in patients with non-infectious AU.

Methods
Patients with non-infectious AU treated with the monoclonal TNF-α inhibitors IFX, ADA, GOL and CZP because of persistent or severe inflammation or owing to the need of quick steroid tapering were enrolled in the present study. Their demographic, clinical and therapeutic data were retrospectively collected. Biologic agents were administered at the standard doses approved for on-label use. Patients suffering from BS, SpA, psoriatic arthritis, and JIA were diagnosed according to the international criteria currently available. Anatomical classification of anterior uveitis along with the specific course of ocular inflammation (acute, recurrent or chronic) were assessed according to the Standardisation of Uveitis Nomenclature (SUN) working group criteria (13). Before starting TNF-α inhibition a full infectious disease screening was performed in order to rule out tuberculosis, hepatitis B or C infection, HIV infection, and *Toxoplasma gondii* infection. Cardiac diseases and malignant conditions were also excluded. According to the best standard of care, all patients were evaluated every three months or in case of relapse or safety concerns by both the rheumatologist and the ophthalmologist.

All patients had to be managed for at least 12 months before starting the study treatments.

Data recorded included: age, gender, age at disease onset, age at uveitis onset, laterality of uveitis, rate of uveitis recurrence, ocular complications, any systemic diagnosis, the specific TNF-α inhibitor administered, treatment duration, previous and concomitant treatments, adverse events and ocular complications identified during the follow-up period. Best corrected visual acuity (BCVA) and corticosteroid dosages at the start of therapy, at the 12-month follow-up and at the last follow-up visit were also collected.

The primary aim of the study was to evaluate the efficacy of monoclonal anti-TNF-α agents in reducing the re-

currence rate of AU flares. The secondary aims were: i) to identify any demographic, clinical or therapeutic variable associated with a sustained response to monoclonal TNF-α inhibitors among patients with AU; ii) to assess the variation of BCVA during follow-up; iii) to evaluate the role of TNF-α inhibitors as corticosteroid sparing agents among patients with AU; iv) to assess the safety profile of treatments studied and the ability of treatments in preventing the onset of ocular complications.

The primary endpoint was represented by a statistically significant decrease in the amount of ocular flares expressed as number of events/100 patients/year assessed during the whole follow-up period and compared to the 12 months preceding the start of TNF-α blockers. Secondary endpoints were as follows: i) to identify any clinical, therapeutic or demographic variable significantly associated with long-term treatment by using linear regression analysis; ii) to identify statistically significant changes in BCVA between the last or the 12-month assessment visit and the start of therapy; iii) to evaluate a statistically significant decrease in the number of patients concomitantly treated with corticosteroids at the 12-month visit and at the last follow-up visit compared to baseline; iv) to report adverse events and ocular complications occurred during the follow-up.

Descriptive statistics was performed for sample size, percentages, mean, interquartile range (IR) and standard deviation (SD). Pair wise computations were performed by using 2x3 contingency tables for qualitative variables and ANOVA or Kruskal-Wallis test (as required) for quantitative variables. Post-hoc analysis was performed by using Fisher's exact test for qualitative data and Mann-Whitney U-test or Student's *t*-test (as required). Bonferroni correction was also applied at post-hoc analysis. Linear regression analysis was used to identify variables associated with long-term response. Statistical Package for Social Science (SPSS) 24.0 software was used for statistical computations. Significance was defined as $p<0.05$.

This study was conformed to the tenets of Declaration of Helsinki and the

protocol was approved by the local Ethic Committee (AOUS, Azienda Ospedaliera Universitaria Senese, Siena, Italy). Written informed consent was obtained from all patients or their legal guardians.

Results
Sixty-nine patients (22 males, 47 females) were enrolled in this study: their demographic, clinical and therapeutic features are summarised in Table I.

Unilateral and bilateral ocular involvement was described in 37 (53.6%) and 32 (46.4%) cases, respectively. Altogether, 101 eyes were affected by AU. An associated systemic disease was identified in 64 cases (92.8%); conversely, 5 patients (7.2%) suffered from idiopathic AU (8 eyes). Anterior uveitis was classified as acute in 47 (68.1%) patients, recurrent in 16 (23.2%) and chronic in 6 cases (8.7%). Fifty-eight patients (84.1%) had undergone biologic treatment because of systemic disease activity, and 11 patients (15.9%) had started biologic agents due to persistent eye inflammation.

The mean treatment duration was 29.25±23.51 (range: 1-123) months. During the 12 months preceding the start of monoclonal TNF-α inhibitors, 29 ocular flares were recorded accounting for 42.03 flares/100 patients/year; during the entire follow-up period, 5 ocular flares were reported, accounting for 2.9 flares/100 patients/year. The decrease in ocular flares after the start of TNF-α inhibition amounted to 93.1% ($p<0.0001$). Ocular flares occurred while on ADA treatment in all cases during follow-up.

At linear regression analysis, concomitant treatment with cDMARDs represented the sole clinical, demographic or therapeutic variable associated with treatment duration in the long-term ($p=0.045$, $R^2=0.87$).

No differences were identified between the BCVA values collected at baseline (8.7±2.4, IR=8-10), 3-month follow-up visit (mean±SD=8.7±2.5, IR=8.5-10), 12-month visit (mean±SD=8.7±2.5, IR=8-10), and last follow-up visit (mean ±SD=8.86±1.7, IR=8-10) ($p>0.99$).

The number of patients treated with corticosteroids was significantly higher

at baseline compared with that identified at the 12-month assessment (43 *vs*. 20 patients, *p*<0.001) and at the last follow-up visit (43 *vs*. 26 patients, *p*=0.006). No statistically significant differences were identified in the number of patients treated with systemic corticosteroids between the 12-month evaluation and the last follow-up visit (26 *vs*. 20 patients, *p*=0.39). No statistically significant changes were identified in the mean daily corticosteroid dosage administered during the study period (*p*=0.38).

As a whole, 31 patients discontinued TNF-α inhibition during the follow-up. In particular, 4 (5.8%) patients discontinued treatments within the 3-month assessment and 14 (20.3%) within the first 12 months of treatment. Reasons for discontinuation were as follows: 8 adverse events, 8 lack of efficacy over systemic disease activity, 7 loss of efficacy over systemic disease activity, 5 loss of compliance, 3 loss at follow-up. Adverse events included infectious events (n=2), anaphylaxis (n=1), atopic skin reactions (n=1), alopecia (n=1), eczematous skin rash (n=1), skin ulceration (n=1), tremor and myoclonus (n=1). The overall rate of adverse events leading to treatment discontinuation was 4.75/100 patients/year.

Regarding ocular complications during follow-up, new posterior ocular synechiae were identified in 1 patient (2 eyes) treated with CZP; glaucoma was recognised in 2 patients (3 eyes) respectively treated with ADA and GOL; lens opacity was observed in 3 cases (3 eyes), two of which treated with ADA and one with GOL. Table II summarises clinical variables assessed at different time points during the follow-up period.

Discussion

TNF-α inhibition has been recently suggested as a successful treatment option for patients with non-infectious AU (2, 4-12). The present study confirms previous findings on a cohort of patients suffering from recurrent AU and treated with monoclonal TNF-α inhibitors. In particular, the present study highlights the exceptional ability of monoclonal TNF-α inhibitors in reducing the rate of AU flares and avoid-

ing ocular complications. Specifically, the recurrence of AU decreased more than 90% after the start of monoclonal TNF-α blockers when compared with the 12 months immediately preceding treatment. This finding is more remarkable than that reported by other authors (14, 15). In particular, Rudwaleit *et al*. (14) identified a decrease of AU flares by 68% in 274 patients with SpA treated with ADA, while van Denderen *et al*. (15) reported an 80% reduction rate in the first year of ADA treatment. However, in the present study the percentage of patients concomitantly treated with cDMARDs and corticosteroids

at baseline was much higher than those reported by previous authors (14, 15). This difference could explain the better results obtained in our patients in terms of control of AU recurrence. Accordingly, in our study the concomitant use of cDMARDs accounted for the only demographic, clinical or therapeutic factor significantly associated with long-term treatment duration with monoclonal TNF-α inhibitors. This finding seems to highlight a role of cDMARDs in the routinely management of patients with resistant AU and is in agreement with previous results obtained by Vallet *et al*. (9), who iden-

Table I. Summary of demographic, clinical and therapeutic features of patients enrolled in this study.

Features	Outcome
Male/female patients	22/47
Age at enrollment, years (mean ± SD)	44.86 ± 12.38
Age at uveitis onset, years (mean ± SD)	34.00 ± 15.9
Duration of uveitis, years (mean ± SD)	10.73 ± 9.89
Age at systemic disease onset, years (mean ± SD)	30.31 ± 16.31
Duration of systemic disease (mean ± SD)	12.11 ± 9.61
Systemic diseases identified	
Behçet's syndrome, n (%)	31 (44.93)
Spondyloarthritis, n (%)	24 (34.78)
Juvenile idiopathic arthritis, n (%)	6 (8.7)
Psoriatic arthritis, n (%)	2 (2.9)
HLA-B27 associated uveitis	1 (1.4)
Monoclonal TNF-α inhibitor administered	
Adalimumab, n (%)	42 (60.9)
Infliximab, n (%)	12 (17.4)
Golimumab, n (%)	8 (11.6)
Certolizumab, n (%)	7 (10.1)
Previous treatments	
Corticosteroids, n (%)	63 (91.3)
cDMARDs, n (%)	47 (68.1)
Methotrexate, n	31
Cyclosporine, n	19
Azathioprine, n	7
Mycophenolate mofetil, n	1
Biologic agents, n (%)	26 (37.7)
Infliximab, n	14
Adalimumab, n	12
Etanercept, n	9
Golimumab, n	3
Certolizumab pegol, n	1
Anakinra, n	1
Rituximab, n	1
Concomitant treatments at baseline	
Systemic corticosteroids, n (%)	43 (62.3)
cDMARDs, n (%)	28 (40.6)
Methotrexate (7.5-25 mg/week), n	19
Cyclosporine A (2.5 mg/kg/day), n	8
Sulfasalazine (2 g/day), n	2
Azathioprine (2.5 mg/kg/day), n	1

cDMARDs: conventional disease-modifying anti-rheumatic drugs; HLA: human leukocyte antigen; SD: standard deviation; n: number; TNF: tumour necrosis factor.

Table II. Summary of clinical variables assessed during the whole follow-up period.

	Baseline	3-month follow-up	12-month follow-up	Last follow-up visit
Number of patients treated, n (%)	69 (100)	65 (94.2)	55 (79.7)	38 (55.1)
BCVA values, IR	8-10	8.5-10	8-10	8-10
Lack of efficacy, cumulative n (months, mean±SD)	-	1	8 (7.4 ± 2.7)	8 (7.4 ± 2.7)
Loss of efficacy, cumulative n (months, mean±SD)	-	-	0	7 (41.1 ± 24.8)
Patients taking systemic corticosteroids	43 (62.3)	-	20	26
Systemic prednisone (or equivalent) dosage, mg/day	9.25 ± 6.7	-	6.25 ± 3.9	7.1 ± 7.2
Adverse events, n	-	2	5	8
Ocular complications, eyes	-	-	2: posterior synechiae 2: glaucoma	2: lens opacity 1: glaucoma

BCVA: best corrected visual acuity (Snellen Charts, decimals); IR: 25%-75% interquartile range; n: number; SD: standard deviation.

tified the concomitant use of immuno-suppressive treatment as a factor associated with a complete response to anti-TNF-α agents in patients with uveitis.

In the present study, TNF-α inhibition allowed the preservation of visual acuity during follow-up. Unlike previous experiences (11, 16), we did not identify a statistically significant improvement in BCVA. This is probably due to the relatively preserved visual acuity at baseline, as most of our patients started anti-TNF-α agents because of systemic disease activity rather than ocular inflammation. Nevertheless, our data suggest that early treatment with anti-TNF-α agents may preserve visual acuity in patients with AU and also prevent the onset of sight-threatening complications over time.

The number of patients treated with corticosteroids significantly decreased during follow-up. This is in agreement with previous experiences that judged TNF-α inhibitors as effective steroid-sparing agents (15, 17). Conversely, the mean corticosteroid dosage did not significantly change over time. This was probably due to the high number of patients with SpA treated with low corticosteroid dosage (≤5 mg of prednisone or equivalent) at baseline and during the whole follow-up period. Indeed, according to the international recommendations, SpA treatment does not require corticosteroid administration for joint involvement (18).

During follow-up, the number of adverse events leading to treatment discontinuation was relatively low, suggesting the good safety profile of anti-TNF-α monoclonal antibodies. This finding was slightly higher than that observed by Vallet et al. (9), but lower than that observed in the paediatric sphere (10). Similarly, the rate of ocular complications recorded during follow-up was relatively low and reflected the proper control of ocular inflammation on one hand and the steroid sparing effect on the other.

In the present study, CZP and GOL were used as TNF-α inhibitors as an alternative to ADA and IFX: they both induced favourable results in terms of efficacy and safety, supporting the few data currently available on their promising role in patients with AU (11, 12, 16).

In conclusion, monoclonal TNF-α inhibitors have induced a remarkable decrease in the recurrence rate of AU during a long-term follow-up period, along with a significant steroid sparing effect and stabilisation of visual acuity. Among clinical, demographic or therapeutic features, a concomitant treatment with cDMARDs represented the sole variable associated with treatment duration in the long-term.

Affiliations

¹Department of Ophthalmology, Humanitas Clinical and Research Centre, Rozzano, Milan;
²Ophthalmology Unit, Department of Medicine, Surgery and Neuroscience, University of Siena;
³Research Centre of Systemic Autoinflammatory Diseases and Behçet's Disease and Rheumatology-Ophthalmology Collaborative Uveitis Centre, Department of Medical Sciences, Surgery and Neurosciences, University of Siena;
⁴Institute of Paediatrics, Università Cattolica Sacro Cuore, Fondazione Policlinico Universitario "A. Gemelli", Rome;
⁵Department of Experimental and Clinical Medicine, University of Florence;
⁶Interdisciplinary Department of Medicine, Rheumatology Unit, University of Bari;
⁷Department of Surgery and Translational Medicine, Eye Clinic, University of Florence;
⁸Department of Ophthalmology and Otolaryngology, University of Bari, Italy.

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