Efficacy of monoclonal anti-tumour necrosis factor-α antibodies in uveitic macular oedema

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Abstract

Objective

To assess the efficacy of anti-tumour necrosis factor (TNF)-α agents in the treatment of refractory uveitic macular oedema (UME).

Methods

Patients with refractory UME treated with TNF-α blockers were retrospectively enrolled. Central macular thickness (CMT) was assessed at optical coherence tomography (OCT) at the start of TNF-α inhibition, after 3 and 12 months, and at the last follow-up visit.

Results

Thirty-six patients (56 eyes with UME) were enrolled. The mean follow-up period was 29.9±40.8 (4-184) months. A statistically significant decrease was observed in the frequency of UME ($p<0.0001$) and in the mean CMT values ($p<0.0001$) during the study period. Best corrected visual acuity improved in 35 eyes (62.5%), remained stable in 12 eyes (21.4%), reduced in 9 eyes (16.1%). The mean corticosteroid dosage significantly decreased during the study period ($p=0.016$).

Conclusion

TNF-α inhibitors represent a useful treatment in patients with severe or resistant UME.

Key words

adalimumab, certolizumab, golimumab, infliximab, uveitis.

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Introduction

Uveitic macular oedema (UME) accounts for a retinal thickening in the macular area owing to intra- or sub-retinal fluid accumulation and is the most sight-threatening complication of intraocular inflammation (1). It may occur in more than 30% of patients with uveitis, especially in chronic cases and in patients with intermediate uveitis, posterior uveitis and panuveitis. Nevertheless, UME may also complicate anterior uveitis, especially in case of highly relapsing uveitis and when anterior inflammation spills into the vitreous (2-4). Notably, UME is a primary cause of visual loss in uveitic patients and represents a strong predictor of best corrected visual acuity (BCVA) worsening (5, 6). For these reasons, early diagnosis and appropriate aggressive treatment are strictly required to prevent long-term structural damage and preserve visual function in eyes with UME (1).

Systemic corticosteroids represent the first-line treatment option in patients with bilateral UME or in case of unilateral refractory UME, but conventional disease-modifying anti-rheumatic drugs (cDMARDs) and/or biologic agents may be added as steroid sparing agents and in recalcitrant cases (1). During the last two decades, tumour necrosis factor (TNF)-α inhibitors have shown to be effective in controlling intraocular inflammation and preventing uveitic relapses in refractory cases (7–9). In particular, the monoclonal anti-TNF-α antibodies adalimumab (ADA) and infliximab (IFX) are the most frequently employed agents in the setting of non-infectious uveitis, with ADA being the only biologic agent approved by the Food and Drug Administration and the European Medicines Agency for the treatment of patients with non-infectious intermediate uveitis, posterior uveitis and panuveitis (10, 11).

Although it is recognised that UME may benefit from treatment with TNF-α blockers in different clinical contexts, to date no randomised controlled clinical trial has primarily explored the role of these agents in the management of UME (12-16). In this regard, the main objective of our study was to assess the short- and long-term efficacy of monoclonal anti-TNF-α antibodies in the treatment of UME.

Patients and methods

Patients with refractory UME treated with TNF-α blockers were retrospectively included in the study; infectious and neoplastic diseases had been ruled out before starting biologic treatment. For the study purposes, UME was defined as refractory in case of persistence of macular oedema despite previous standard treatments. In detail, the following monoclonal anti-TNF-α agents were employed: ADA, administered subcutaneously at the dosage of 40 mg every other week; IFX, used intravenously at the dosage of 5 mg/kg every 8 weeks; golimumab (GOL), used subcutaneously every 4 weeks at a dosage of 50 mg; and certolizumab pegol (CZP) initially given subcutaneously at a dosage of 400 mg for induction and then 200 mg fortnightly. The choice of the TNF-α antagonist had been based on physicians' discretion according to the different specific clinical contexts.

Follow-up visits were performed every 3 months or in case of disease relapse and/or safety concerns, according to the best standard of care. Clinical diagnosis of macular oedema was confirmed in all eyes at optical coherence tomography (OCT) and eyes with a central macular thickness (CMT) value >300 μm and evidence of intraretinal fluid or cysts were included in the study. OCT scans were performed on a Carl Zeiss Meditech Cirrus HD-OCT 5000 in all Centres involved. A Macular Cube 512x128 Smart HD Scan and HD 5-line raster scan were acquired for each eye. Best-corrected visual acuity (BCVA) was assessed with Snellen chart in decimal fractions at any visit. Patients undergoing peribulbar injections or intravitreal corticosteroid injections or implants during the three months preceding the start of biologics were excluded from the study.

The primary aim of the study was to assess the effectiveness of anti-TNF-α treatment in the resolution of UME. Resolution of UME was defined as the absence of any clinical and OCT evidence of inflammatory macular oedema. The secondary aims were: i) to search for any BCVA changes and corticosteroid sparing effect in patients with refractory UME treated with TNF-α inhibitors; ii) to evaluate any impact of a concomitant

Table I. A summary of the demographic and clinical features referred to the start of monoclonal anti-TNF-α treatment from patients enrolled in the study.

Age, years (mean±SD)	42.5 ± 13.9
Age at uveitis onset, years (mean±SD)	31.7 ± 15.6
Uveitis duration, years (mean±SD)	10.8 ± 6.6
Age at onset of systemic disease, years (mean±SD)	17.5 ± 16.8
Systemic disease duration, years (mean±SD)	11.3 ± 13.1
Ocular involvement	
Unilateral uveitis	15 (41.7%)
Bilateral uveitis	21 (58.3%)
Unilateral macular oedema	16 (44.4%)
Bilateral macular oedema	20 (55.6%)
Anterior uveitis, eyes	3 (5.4%)
Intermediate uveitis, eyes	4 (7.1%)
Posterior uveitis, eyes	20 (35.7%)
Panuveitis, eyes	29 (51.8%)
Retinal vasculitis, eyes	18 (32.1%)
Diagnosis	
Behçet's disease	20 (55.6%)
Idiopathic uveitis	10 (27.8%)
Spondiloarthritis	3 (8.3%)
JIA	2 (5.6%)
Sarcoidosis	1 (2.8%)

JIA: juvenile idiopathic arthritis; SD: standard deviation.

treatment with cDMARDs and of the different lines of biologic therapy on the decrease of the mean CMT values.

The primary endpoint was represented by a statistically significant decrease in the number of eyes with UME and in the mean CMT values at the 3- and 12-month follow-up and at the last OCT assessment compared with the start of anti-TNF-α treatment (baseline). The secondary endpoints corresponded to: i) a statistically significant improvement of BCVA during follow-up; ii) the identification of a statistically significant decrease between baseline and the last follow-up visit in the number of patients requiring corticosteroids and in the mean corticosteroid dosage used among patients continuing steroids; iii) to search for any statistically significant difference in the CMT value reduction between biologic naïve patients and patients previously treated with other biologics as well as between patients undergoing monotherapy and those concomitantly treated with cDMARDs.

Descriptive statistics was used for percentages, mean values and standard deviation or median and interquartile range, as appropriate. The Shapiro-Wilk test was used to assess normality distribution. For categorical variables, chi square test was used for the overall assessment of changes during follow-up by employing 4x2 contingency tables; *post-hoc* analysis was performed using McNemar test. For qualitative variables, repeated measures ANOVA or Friedman test were used, as required, for the overall assessment during follow-up; *post-hoc* analysis was performed using Student's *t*-test or Wilcoxon test, as appropriate. The threshold for statistical significance was set to $p<0.05$; Bonferroni correction was applied for multiple comparisons as indicated. Data were computed using IBM SPSS Statistics for Windows, v. 24 (IBM Corp., Armonk, N.Y., USA).

Results

Thirty-six patients (23 males, 13 females) corresponding to 56 eyes with refractory UME were enrolled in the study. Table I summarises demographic and clinical data of the patients enrolled, whereas Table II provides detailed information about previous and concomitant treatments.

The mean follow-up period was 29.9±40.8 (4-184) months. The following TNF-α inhibitors were employed: ADA in 23 patients, IFX in 9 patients, CZP in 3 patients and GOL in 1 patient. The number of eyes with UME significantly decreased during the whole follow-up ($p<0.0001$), as better specified in Figure 1A. The number (percentage) of eyes showing UME resolution at 3-months, 12-months and at the last follow-up visit was 14 (25%), 27 (48.2%) and 29 (51.8%), respectively.

The mean CMT was 395.7±98.4 μm (median value=389 μm) at baseline, 380.3±99.4 μm (median value=360 μm) at 3-month follow-up, 326.0±103.3 μm (median value=310 μm) at 12-month assessment and 329.0±108.8 μm (median value=300 μm) at the last follow-up visit. A statistically significant decrease was observed in the mean CMT values during the whole follow-up period ($p<0.0001$). Specifically, statistically significant differences were identified between baseline and 12-month assessment ($p<0.0001$) as well as between 3-month and 12-month follow-up visits ($p<0.0001$). Conversely, Bonferroni correction did not reach statistical significance between baseline and the 3-month visit ($p=0.029$) and no significant differences were found in the mean CMT values between the 12-month evaluation and the last follow-up visit ($p=0.423$). A statistically significant CMT decrease was also observed during the study period in the subgroup of patients with no UME resolution during follow-up ($p=0.002$). These results are shown in Figure 1B.

No statistically significant differences were identified in the decrease of CMT during follow-up between biologic naïve patients and those undergoing their second line (or more) biologic therapy ($p=0.785$). Similarly, no significant differences were identified between patients initially treated with cDMARDs and those firstly treated with TNF-α inhibitors ($p=0.192$). During the whole study period patients concomitantly treated with cDMARDs showed a significantly higher decrease of CMT com-

Table II. Previous and concomitant treatment approaches described in the cohort of patients enrolled.

Previous treatments	
Biologic agents	**13 (36.1%)**
Adalimumab	6
Infliximab	5
Certolizumab	3
Abatacept	2
Golimumab	1
Anakinra	1
cDMARDs	28 (77.8%)
Methotrexate	17
Cyclosporine A	14
Azathioprine	8
Mycophenolate mofetil	4
Cyclophosphamide	2
Sulfasalazine	1
Concomitant treatments at baseline	
Methotrexate	8 (22.2%)
Azathioprine	5 (13.9%)
Cyclosporine A	4 (11.1%)
Mycophenolate mofetil	1 (2.8%)
No concomitant treatment with cDMARDs	18 (50%)
Corticosteroids at the start of treatment	36 (100%)
Concomitant treatments at last follow-up visit	
Methotrexate	7 (19.4%)
Azathioprine	4 (11.1%)
Cyclosporine A	3 (8.3%)
Corticosteroids at the last follow-up	23 (63.9%)

cDMARDs: conventional disease-modifying anti-rheumatic drugs.

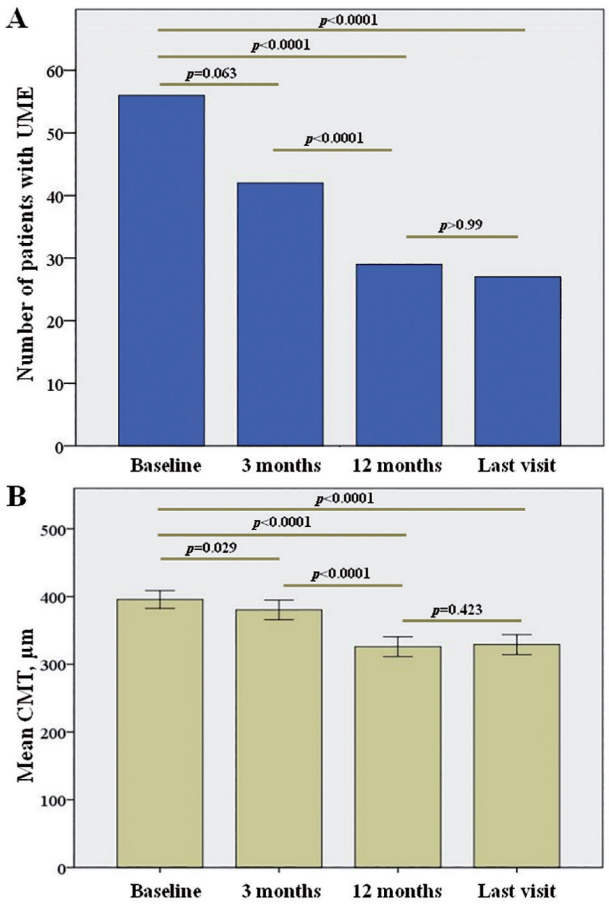

Fig. 1. The number of patients with uveitic macular oedema (UME) (**A**) and the mean central macular thickness (CMT) (**B**) at the start of monoclonal anti-TNF-α treatment (baseline), after 3 and 12 months of therapy and at the last follow-up visit. The *p*-values provided were obtained using the McNemar test.
The bars in **B** represent one standard error of the mean; significance after Bonferroni correction for multiple comparisons $p<0.01$.

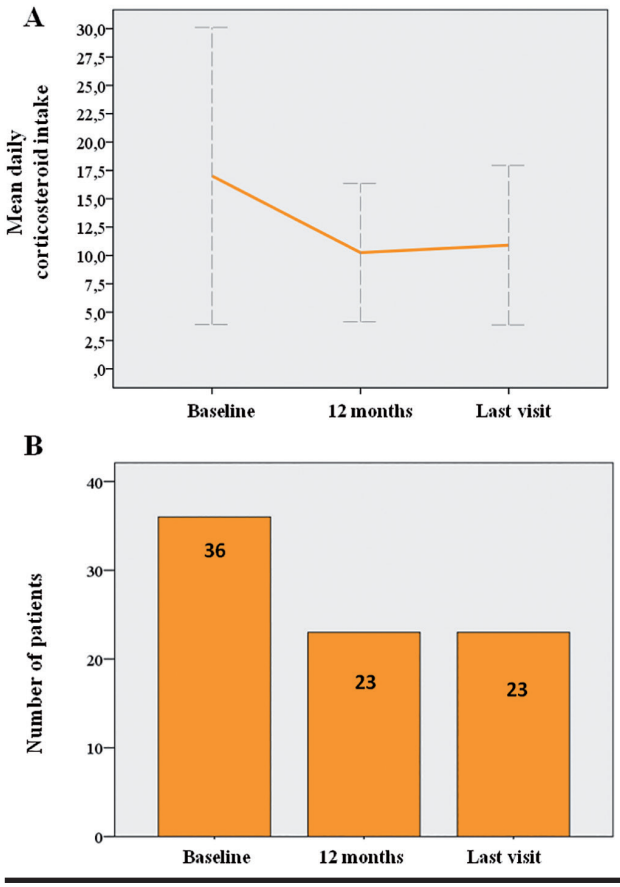

Fig. 2. The mean daily corticosteroid dosage (prednisone or equivalent) among patients treated with steroids (**A**) and the number of patients undergoing corticosteroid administration (**B**) at baseline, at 3-month assessment and at the last follow-up visit.
The error bars in **A** refer to ±1 standard deviation; the numbers specified in the histograms of **B** specifically indicate the total number of patients treated with corticosteroids.

pared to patients undergoing TNF-α inhibitors as monotherapy ($p=0.012$).
No significant differences between patients diagnosed with a systemic disease compared with subjects suffering from idiopathic uveitis ($p=0.226$).
The mean BCVA value was 0.69±0.25 (median value=0.7) at the start of treatment and 0.74±0.31 (median value=0.9) at the last follow-up visit ($p=0.065$); BCVA improved in 35 eyes (62.5%), remained stable in 12 eyes (21.4%), reduced in 9 eyes (16.1%).
With regard to the corticosteroid sparing effect, a statistically significant decrease in the frequency of patients treated with corticosteroids was identified between the start of treatment and the last follow-up visit ($p<0.0001$). The mean corticosteroid dosage was significantly lower at the last follow-up visit among patients continuing corticosteroids throughout the study period ($p=0.016$). These findings have been graphically provided in Figure 2.
Concerning uveitic complications, at baseline epiretinal membranes and retinal atrophy were identified in 10 eyes (17.9%) and in 1 eye respectively. During follow-up, lens opacity developed in 9 eyes (16.1%) and transient intraocular hypertension was observed in 9 eyes (16.1%).

Discussion

During the last few years, anti-TNF-α agents have shown to be an effective treatment option for patients with non-infectious uveitis, including severe or resistant cases (7-15, 17). Likewise, TNF-α inhibitors may be also effective in patients with long-standing refractory UME, which has been found to resolve in 50% to 70% of cases despite the concomitant tapering of cDMARDs and corticosteroids (7, 18-21).
The present study was specifically designed to evaluate the efficacy of TNF-α inhibitors in eyes with UME. In agreement with previously reported studies we have confirmed the sustained efficacy of monoclonal TNF-α inhibitors in counteracting refractory UME. In detail, a statistically significant decrease in both the CMT values and the frequency of UME was observed during the first 12 months of therapy. Clinical efficacy

persisted over the first year of treatment, during the whole follow-up period. Conversely, UME improvement did not reach statistical significance within the first 3 months of treatment, suggesting a high but not prompt efficacy of monoclonal anti-TNF-α agents in resolving or ameliorating UME. This is in contrast with the results reported by Schaap-Fogler *et al*. (19) who identified a significant reduction of CMT as early as 1 month of treatment. This discrepancy could be related to the different disease and biologic agents distribution between the two cohorts of patients, the higher number of patients enrolled in our study and the different statistical method.

The percentage of UME resolution reported in our study is in line with previous literature data (18, 20). Indeed UME completely resolved in approximately half of affected eyes within the last assessment. Nevertheless, the primary endpoint of our study was met, thus supporting that the use of TNF-α inhibitors may represent an effective treatment approach also in severe clinical contexts. In this regard, the mean CMT values were slightly above normal ranges at the last study assessment. Of note, the primary objective of the study was achieved despite almost 20% of eyes showed exudative UME and epiretinal membrane at baseline, which competed against the estimation of drug efficacy.

It is noteworthy that the efficacy of TNF-α antagonists on UME was similar disregarding the different lines of biologic treatment and the use of TNF-α blockers prior to cDMARDs. Conversely, the concomitant use of cDMARDs and anti-TNF-α agents led to significantly better results than those observed in patients undergoing monotherapy with biologics. As a whole, these results support an early aggressive combination therapy in refractory cases.

As for previous experiences with non-infectious uveitis treated with TNF-α blockers (18, 21), we also identified a significant corticosteroid sparing effect with a large percentage of patients discontinuing corticosteroids and the remaining patients undergoing significantly lower corticosteroid dosages. Concerning BCVA improvement, we observed only a trend toward statistical significance. This finding is in contrast with previous studies supporting the significant improvement of visual acuity in patients with UME undergoing TNF-α inhibition (19). To a large extent, this is probably related to the high number of patients presenting with uveitic ocular complications at baseline, as expression of a severe long-standing intraocular inflammation. Actually, a non-negligible percentage of eyes included in the study was already affected by epiretinal membranes and retinal atrophy at the start of treatment. Moreover, a further percentage of eyes developed cataract within the end of the study. As a whole, these complications have presumably affected the BCVA improvement at least partially in our cohort of patients and should address to an early and aggressive immunosuppressive treatment of UME.

The results obtained in the present study support the use of TNF-α inhibitors as a useful treatment choice for patients with refractory UME, in addition to currently available therapeutic opportunities including systemic and loco-regional corticosteroids administrations.

In conclusion, monoclonal TNF-α inhibitors represent an effective treatment approach in eyes with refractory UME both in terms of morphological and functional outcomes, disregarding the different line of biologic therapy. In addition, in the most severe cases a combination therapy with cDMARDs may be required to obtain a better outcome.

References

1. FARDEAU C, CHAMPION E, MASSAMBA N, LEHOANG P: Uveitic macular edema. *Eye (Lond)* 2016; 30: 1277-92.
2. BODAGHI B, CASSOUX N, WECHSLER B *et al*.: Chronic severe uveitis: etiology and visual outcome in 927 patients from a single center. *Medicine* (Baltimore) 2001; 80: 263-70.
3. DE SMET MD, OKADA AA: Cystoid macular edema in uveitis. *Dev Ophthalmol*. 2010; 47: 136-47.
4. LOPALCO G, VENERITO V, SOTA J *et al*.: Epidemiological profile of non-infectious uveitis from the rheumatologist's perspective: a survey from two tertiary referral centres in Italy. *Clin Exp Rheumatol* 2018; 36: 68-73.
5. TOMKINS-NETZER O, TALAT L, BAR A *et al*.: Long-term clinical outcome and causes of vision loss in patients with uveitis. *Ophthalmol* 2014; 121: 2387-92.
6. KEMPEN JH, VAN NATTA ML, ALTAWEEL MM *et al*.: Factors predicting visual acuity outcome in intermediate, posterior, and panuveitis: The Multicenter Uveitis Steroid Treatment (MUST) Trial. *Am J Ophthalmol* 2015; 160: 1133-41.e9.
7. FABIANI C, VITALE A, RIGANTE D *et al*.: Comparative efficacy between adalimumab and infliximab in the treatment of non-infectious intermediate uveitis, posterior uveitis, and panuveitis: a retrospective observational study of 107 patients. *Clin Rheumatol* 2019; 38: 407-15.
8. FABIANI C, VITALE A, RIGANTE D *et al*.: Predictors of sustained clinical response in patients with Behçet's disease-related uveitis treated with infliximab and adalimumab. *Clin Rheumatol* 2018; 37: 1715-20.
9. FABIANI C, VITALE A, EMMI G *et al*.: Long-term retention rates of adalimumab and infliximab in non-infectious intermediate, posterior, and panuveitis. *Clin Rheumatol* 2019; 38: 63-70.
10. AbbVie International. Prescribing information Humira. http://www.rxabbvie.com/pdf/humira.pdf; 2017.
11. Humira 40 mg/0.4 ml Pre-filled Syringe and Pre-filled Pen - Summary of Product Characteristics (SmPC) - (eMC). https://www.medicines.org.uk/emc/medicine/31860
12. MARKOMICHELAKIS NN, THEODOSSIADIS PG, PANTELIA E, PAPAEFTHIMIOU S, THEODOSSIADIS GP, SFIKAKIS PP: Infliximab for chronic cystoid macular edema associated with uveitis. *Am J Ophthalmol* 2004; 138: 648-50.
13. BARRY RJ, TALLOUZI MO, BUCKNALL N *et al*.: Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis. *Cochrane Database Syst Rev* 2018; 12: CD012577.
14. MACKENSEN F, HEINZ C, JAKOB E *et al*.: Randomized controlled study to evaluate the efficacy of adalimumab in patients with different forms of refractory uveitis. *Ocul Immunol Inflamm* 2018; 26: 1015-22.
15. PALMOU-FONTANA N, CALVO-RÍO V, MARTÍN-VARILLAS JL *et al*.: Golimumab in refractory uveitis associated to juvenile idiopathic arthritis: multicentre study of 7 cases and literature review. *Clin Exp Rheumatol* 2018; 36: 652-7.
16. SOTA J, VITALE A, FABIANI C *et al*.: The eye involvement in monogenic autoinflammatory diseases: literature review and update. *Clin Exp Rheumatol* 2018; 36: 44-53.
17. TOSI GM, SOTA J, VITALE A *et al*.: Efficacy and safety of certolizumab pegol and golimumab in the treatment of non-infectious uveitis. *Clin Exp Rheumatol* 2019; 37: 680-83.
18. DÍAZ-LLOPIS M, SALOM D, GARCIA-DE-VICUÑA C *et al*.: Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. *Ophthalmology* 2012; 119: 1575-81.
19. SCHAAP-FOGLER M, AMER R, FRILING R, PRIEL E, KRAMER M: Anti-TNF-α agents for refractory cystoid macular edema associated with noninfectious uveitis. *Graefes Arch Clin Exp Ophthalmol* 2014; 252: 633-40.
20. DIAZ-LLOPIS M, GARCÍA-DELPECH S, SALOM D *et al*.: Adalimumab therapy for refractory uveitis: a pilot study. *J Ocul Pharmacol Ther* 2008; 24: 351-61.
21. DOBNER BC, MAX R, BECKER MD *et al*.: A three-centre experience with adalimumab for the treatment of non-infectious uveitis. *Br J Ophthalmol* 2013; 97: 134-8.