Effectiveness of TNF-α blockade in the treatment of refractory non-infectious scleritis: a multicentre study

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Abstract

Objective

To evaluate the efficacy of tumour necrosis factor (TNF)-α inhibitors in refractory non-infectious scleritis.

Methods

We carried out a retrospective study assessing the efficacy of TNF-α inhibitors in the treatment of scleritis, scleritis relapses, glucocorticoid (GC)-sparing effect, impact on best-corrected visual acuity (BCVA) and safety profile.

Results

Nineteen patients (28 eyes) were eligible for analysis. Scleritis inflammatory grading significantly improved from baseline to the last follow-up (median ± IQR 2±4 and 0±0 respectively, p=0.0006). Scleritis relapses significantly decreased between the 12 months preceding and following biologic therapy (p=0.001). Mean GC dosage decreased from baseline (19.00±13.56 mg) to the last follow-up (7.59±5.56 mg) (p=0.003). No significant differences regarding BCVA were observed. Two AEs were recorded (1 severe urticaria and 1 case of pneumonia and paradoxical psoriasis).

Conclusion

TNF-α inhibitors are effective in the treatment of scleritis while allowing a GC-sparing effect and preserving BCVA.

Key words

scleritis, therapy, biologics, TNF-α inhibitors, intraocular inflammation

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Introduction

The term scleritis refers to a wide spectrum of conditions ranging from mild scleral inflammation to sight-threatening ocular tissue inflammation, which might compromise visual function and threaten the anatomical integrity of the ocular globe (1-5).

The treatment of scleritis is challenging, especially in severe and refractory cases that require high dose systemic glucocorticoids (GCs) and immunosuppressive therapy with disease-modifying anti-rheumatic drugs (DMARDs) (6). The goal of treatment is to suppress scleral inflammation and to maintain a long-term disease remission, thus preventing irreversible functional and structural sequelae. The troublesome task in managing scleritis reflects the not fully understood and complex immunopathogenesis of scleritis, which is likely a result of the interplay between numerous cells, and components of both innate and adaptive immunity (1). Immunologic investigations have revealed the prominent role of T and B cells as well as cytokines such as tumour necrosis factor (TNF)-α, which seem to be of paramount importance in the inflammatory cascade of scleritis and a major driver in tissue damage (1). Altogether, these findings have paved the way to novel and successful strategies for the management of this sight-threatening condition. Evidence on the efficacy and safety of TNF-α inhibitors relies on case reports and small case series (7). Recently, Ragam *et al*. have reported a large series of patients with non-infectious, non-necrotising refractory scleritis and found that the anti-TNF-α agents were able to reduce scleral inflammation and to concomitantly reduce the use of systemic GCs (8). We report herein our multicentre experience on the treatment of refractory non-infectious scleritis with monoclonal anti-TNF-α antibodies.

Patients and methods

Study participants and screening methodology

We conducted a retrospective analysis of patients affected by scleritis and treated with TNF-α inhibitors attending four tertiary ophthalmologic and rheumatologic referral centres for the management and treatment of inflammatory ocular and systemic diseases. Patients were treated with TNF-α inhibitors for active non-infectious refractory (unresponsive to previous treatments, *i.e*. at least one conventional or biologic disease-modifying anti-rheumatic drug) scleritis and/or uncontrolled associated systemic disease. The study was approved by the Local Ethic Committee (Azienda Ospedaliera Universitaria Senese, Siena, Italy) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained by all study participants. Chest radiography, Mantoux or QuantiFERON tests, markers for HBV, HCV, HIV, syphilis, Borrelia burgdorferi serology and urine culture were performed before starting the anti-TNF-α agents, to rule out any latent or active infection. Also cardiac and malignant conditions were ruled out. Infliximab was administered with different regimens ranging from 5 mg/kg every 4 or 8 weeks to 10 mg/kg every 8 weeks whereas adalimumab was given at the standard dose of 40 mg every other week, and golimumab at a dose of 50 mg every 4 weeks. The following demographic, clinical and therapeutic data were collected: age, gender, age at scleritis onset, disease duration, scleritis relapses, adverse events (AEs), ocular complications, preceding biologics and conventional DMARDs as well as local or systemic GCs. According to the best standard of care, patients were regularly examined every 3 months and in case of necessity (AEs or disease relapse) by either the ophthalmologist or the rheumatologist.

Ophthalmologic and systemic work-up

All patients provided a detailed medical history and underwent a complete ophthalmologic examination and systemic work-up. More in detail, ophthalmic examination included best-corrected visual acuity (BCVA), measurement of intraocular pressure, complete slit lamp examination, fundus examination to exclude any posterior segment involvement including macular oedema, retinal vasculitis, retinal detachment, choroidal inflammation, choroidal detach-

ment and/or optic nerve involvement. Anatomical patterns of scleritis were classified in accordance to the scheme proposed by Watson and Hayreh (9). Scleral inflammation was evaluated according to the scleritis grading system proposed by Sen *et al*., where 0 represents no scleral inflammation and 4+ represented the most severe form of scleral inflammation, necrotising scleritis (10). Scleritis quiescence was defined as inflammation grading of 0 on slit-lamp examination and lack of suggestive symptoms. Control of inflammation was defined as a scleritis quiescence for at least 2 months duration (8). Optical coherence tomography was performed to establish any morphologic macular change at a retinal and choroidal level. Ocular ultrasonography and/or orbit magnetic resonance (MR) scan were performed to confirm the diagnosis of posterior scleritis. An extensive multidisciplinary work-up was performed to investigate for a potential underling systemic disease.

Aims and endpoints

The primary aim of our study was to evaluate the efficacy of monoclonal TNF-α inhibitors on scleritis. Secondary aims were to: (i) evaluate any change in the number of scleritis relapses; (ii) evaluate the GC-sparing effect of biologic treatment; (iii) assess the impact of biologic therapy on visual acuity; (iv) determine the safety profile of treatment and to asses any potential ocular complication during treatment. The ancillary aim was represented by the evaluation of the cumulative drug retention rate of TNF-α inhibitors during the whole follow-up period.

The primary endpoint was based on the changes of scleral inflammation during the study period. Secondary endpoints were as follows: (i) to evaluate any potential significant differences on the number of scleritis relapses defined as new onset of ocular disease activity after remission, between the 12 months preceding and the 12 months following the introduction of TNF-α inhibitor (patients with less than 12 months of follow-up were excluded); (ii) to evaluate the impact of TNF-α inhibition on the mean daily dose of prednisone (or equivalent) during the study period; (iii) to detect any significant differences on BCVA assessed on Snellen chart by decimal fractions; (iv) record AEs and serious AEs as well as ocular complications occurred during biologic treatment. Finally, the cumulative drug retention rate was analysed by studying the Kaplan-Meier curve on the whole cohort of patients treated with TNF-α inhibitors.

Table I. Demographic and clinical features of our cohort of 19 patients.

Demographic data	Mean ± SD
Age (years)	45.83 ± 10.42
Age at scleritis onset (years)	41.33 ± 14.87
Disease duration (years)	3.91 ± 3.17
HLA (n)	HLA-B51 (3)
	HLA-B35 (2)
Eye disease	number of eyes
Anterior diffuse scleritis	14 (43.75%)
Anterior nodular scleritis	6 (18.75%)
Anterior necrotising scleritis	4 (12.5%)
Posterior scleritis	8 (25%)
Concomitant uveitis	8 (6 AU, 1 PanU, 1 papillitis; 2 eyes had also IU)
Associated keratitis	4 PUK-peripheral ulcerative keratitis
Associated systemic disease	number
Rheumatoid arthritis	5
Psoriatic arthritis	4
Behçet's syndrome	3
Idiopathic	3
Relapsing polychondritis	1
Takayasu's arteritis	1
Peripheral spondyloarthritis	1
Crohn's disease	1

AU: anterior uveitis; HLA: human leukocyte antigen; IU: intermediate uveitis; PanU: panuveitis; SD: standard deviation.

Statistics

Data were analysed using IBMSPSS Statistics for Windows, v. 24 (IBM Corp., Armonk, NY, United States). Descriptive statistics was employed to display mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Data distribution was assessed by Shapiro-Wilk test. Ordinal data with repeated measures were computed with Friedmann test followed by *post-hoc* Wilcoxon rank sum test. Means were compared by Kruskal-Wallis test with *post-hoc* Mann-Whitney U test. Results regarding *post-hoc* tests were evaluated after Bonferroni correction. Survival analysis was carried out with Kaplan-Meier test, with the event being drug discontinuation. The threshold for statistical significance was set to $p<0.05$ and all p-values were two sided.

Results

A total of 19 consecutive patients (28 eyes) attending clinics from January 2017 to January 2019 were enrolled in the study and retrospectively analysed. Fourteen out of 19 patients (74%) were female. Except for one Hispanic patient, all were Caucasian. Mean age of our cohort was 45.83±10.42 years. Mean treatment duration was 18.00 ± 16.12 months. Detailed demographic information, alongside ocular diagnosis, associated systemic disease and treatment history of the enrolled patients are summarised in Table I and II, respectively.

Ten patients had unilateral scleritis while 9 patients had bilateral involvement. The anatomical pattern of scleritis was established as anterior nodular in 6 eyes, anterior diffuse in 12 eyes, anterior necrotising in 2 eyes, anterior diffuse and posterior in 2 eyes, anterior necrotising and posterior in 2 eyes, and posterior scleritis in 4 eyes. Figure 1 shows magnetic resonance imaging and ocular ultrasonographic findings in a patient with active idiopathic posterior scleritis. Sixteen out of 19 patients were found to have an associated systemic disease. The most commonly diagnosed systemic disorder was rheumatoid arthritis (5/19) followed by psoriatic arthritis (4/12) and Behçet's syndrome (3/19). Three patients (5 eyes) present-

Table II. Past and current therapies of enrolled patients.

Previous treatments	n
Loco-regional corticosteroids	8
cDMARDs	31
Methotrexate	13
Azathioprine	6
Cyclosporine A	5
Cyclophosphamide	2
Mycophenolate mofetil	2
Sulfasalazine	2
Hydroxychloroquine	1
Previous Biologics	10
Adalimumab	3
Infiliximab	2
Rituximab	2
Anakinra	1
Abatacept	1
Etanercept	1
Ongoing treatment	n
cDMARDs	14
Methotrexate	10
Cyclosporine A	2
Azathioprine	1
Mycophenolate mofetil	1
Biologic agent	*19*
Adalimumab	13
Infliximab	5
Golimumab	1

cDMARDs: conventional disease-modifying anti-rheumatic drugs.

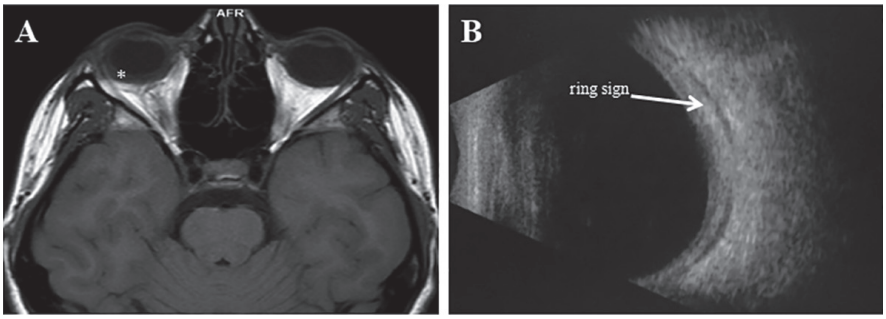

Fig. 1. A: Magnetic resonance imaging (MRI) showing a thickened rim of hypointensity on T1 weighted images scan at a choroidal and scleral level in the right eye (*) affected by active posterior scleritis. **B**: Ocular ultrasonography of the right eye of a patient affected by idiopathic active posterior scleritis: ultrasonography shows a circular acoustically hollow area called the ring sign corresponding to an oedematous Tenon capsule.

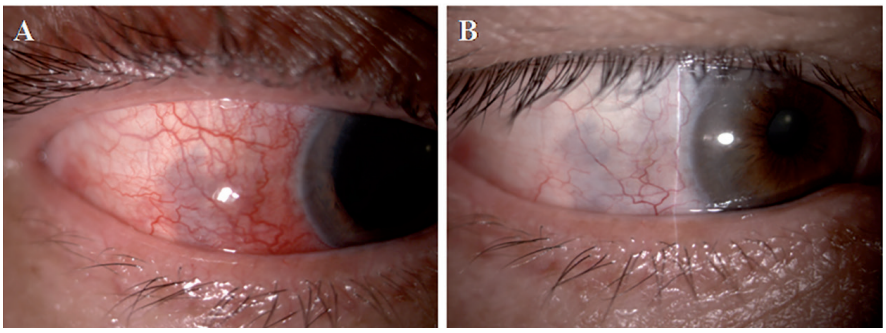

Fig. 2. A: Active anterior nodular scleritis of the right eye of a patient affected by rheumatoid arthritis. **B**: Resolution of the anterior nodular scleritis following 2 months treatment with tumour necrosis factor (TNF)-α inhibitor adalimumab.

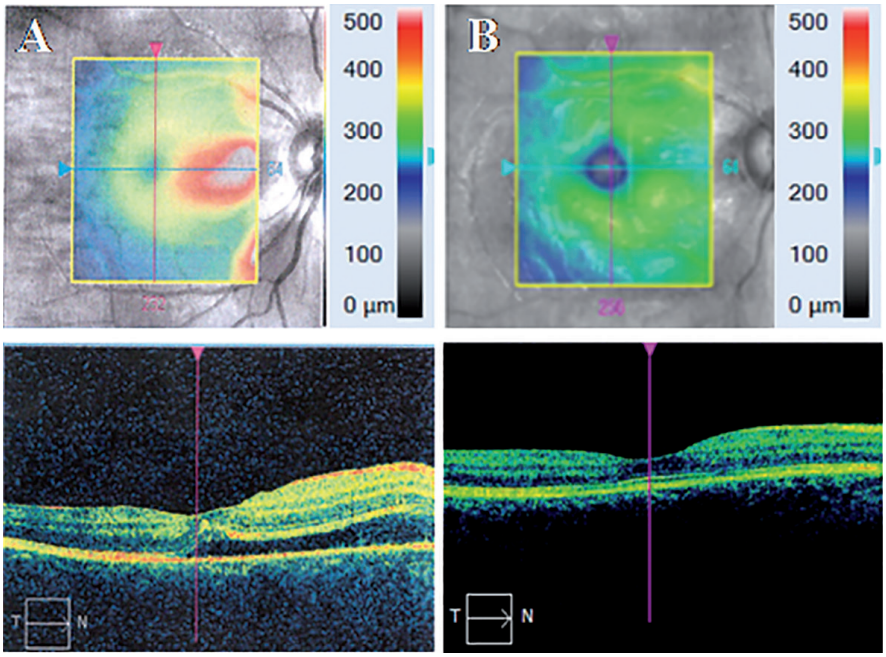

Fig. 3. Optical coherence tomography of a patient affected by idiopathic posterior scleritis. **A**: Exudative retinal detachment in the right eye during the acute phase. **B**: Resolution of the exudative retinal detachment in the same eye under biologic treatment.

ed with no identifiable systemic disease and were therefore classified as having idiopathic scleritis.

The scleritis grade showed a significant decrease during the follow-up period ($p<0.0001$). A significant improvement emerged from baseline to 3 months (median ± IQR 2±4 and 0±1 respectively, $p=0.00059$) and from baseline to the last follow-up visit (median ± IQR 2±4 and 0±0 respectively, $p=0.0006$), while no significant differences were detected between 3 months and the last follow-up visit ($p=0.157$). At baseline, 21 out of 28 eyes had an active scleritis, whereas in 7 eyes scleritis was quiescent. Figure 2 shows the resolution of active anterior nodular scleritis in a patient with rheumatoid arthritis. Figure 3 illustrates the resolution of exudative retinal detachment at optical coherence tomography in a patient affected by idiopathic posterior scleritis. The complete resolution of active scleritis was achieved in 13/21 eyes. Scleritis improved in 4/21 eyes, whereas 4/21 eyes did not improve. In the remaining 7 eyes (quiescent at baseline) scleritis remained stable during the whole follow-up period. Figure 4 illustrates the changes in the scleritis grading from baseline to 3 months and to the last follow-up.

A significant decrease in the number

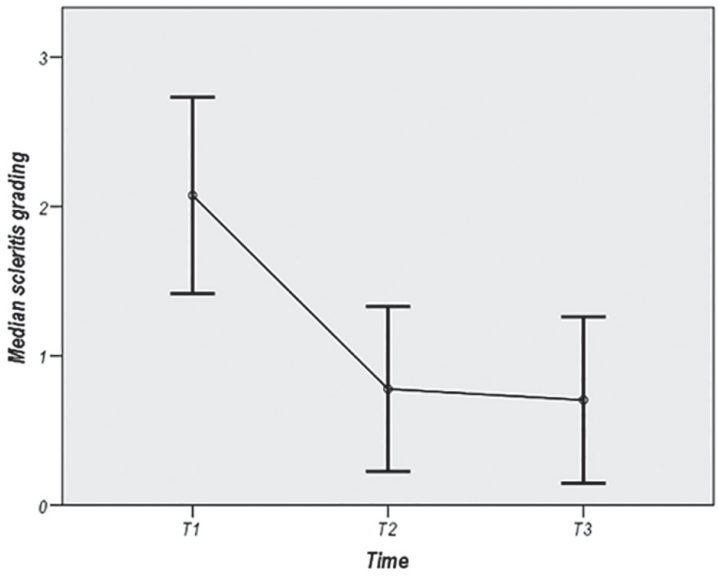

Fig. 4. Trend of median scleritis grading score from baseline (T1) to 3-month (T2) and to the last follow-up visit (T3) in the 28 eyes enrolled.

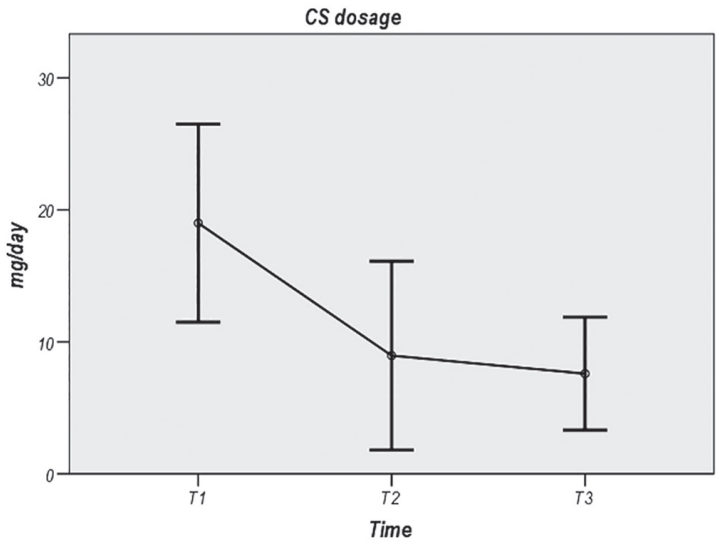

Fig. 5. The progress of mean glucocorticoid (GCs) dosage orally administered at baseline (T1), 12-month (T2) and last follow-up visit (T3).

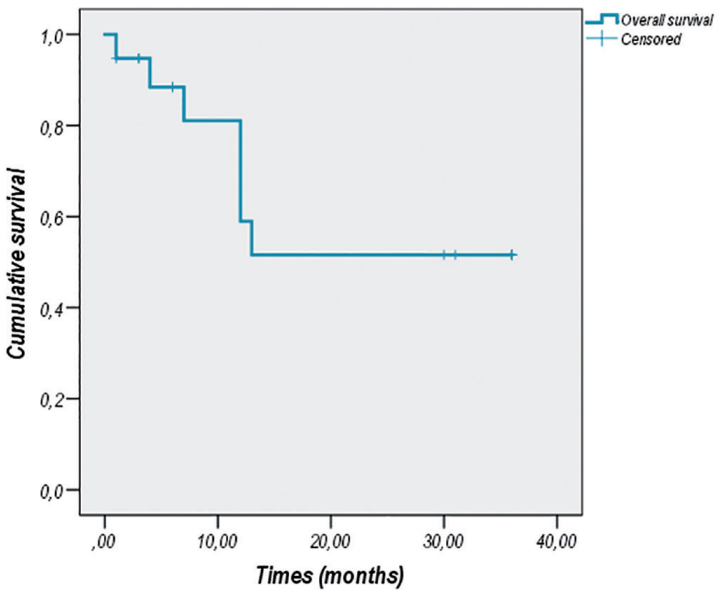

Fig. 6. Kaplan-Meier curve related to the overall cumulative drug retention rate of tumour necrosis factor-α inhibitors in the whole cohort of patients affected by scleritis.

of scleritis relapses was identified between the 12 months preceding and following anti-TNF-α therapy (p=0.001). The mean daily GC dosage decreased from 19.00±13.56 mg at baseline to 8.96±6.81 mg at 12-month follow-up (p=0.034) and from 19.00±13.56 mg at baseline to 7.59±5.56 mg at the last follow-up visit (p=0.0032). Figure 5 illustrates the GC dosage during the study period. Conversely, no differences regarding BCVA were observed between baseline (median ± IQR 10±1.25 and 10±1 respectively) and the last follow-up visit (p=0.678).

The overall drug retention rate of TNF-α inhibitors was 58.9% and 51.6% at 12- and 36-months, respectively (Fig. 6). AEs were responsible for drug discontinuation in 2 patients (1 case of severe urticaria and another case with pneumonia and paradoxical psoriasis). Other 6 patients discontinued treatment (1 for primary failure, 4 for loss of efficacy and 1 for the occurrence of retrobulbar optic neuritis). The following ocular complications were recorded: scleral thinning in 4 eyes, cataract in 1 eye, phthisis bulbi in 2 eyes whereas 1 eye developed epiretinal membrane. Figure 7 shows the development of diffuse scleral thinning in a patient with rheumatoid arthritis and the occurrence of a macular epiretinal membrane in a patient affected by idiopathic posterior scleritis.

Discussion

TNF-α inhibitors have been associated with long-term drug-induced remission of ocular inflammation, preservation of visual acuity and reduction of systemic GC intake. Most of the accrued experienced and reported literature concerning TNF-α inhibitors has mainly focused on uveitis (11-15), while their efficacy and safety in scleritis rely only on case reports and small case series (7).

We report herein a large series of patients affected by refractory anterior and posterior scleritis treated with TNF-α inhibitors. Based on our findings, biologic therapy resulted in a rapid improvement of clinical signs with nearly 60% of eyes achieving a complete control of inflammation within 3 months from the start of treatment. In line

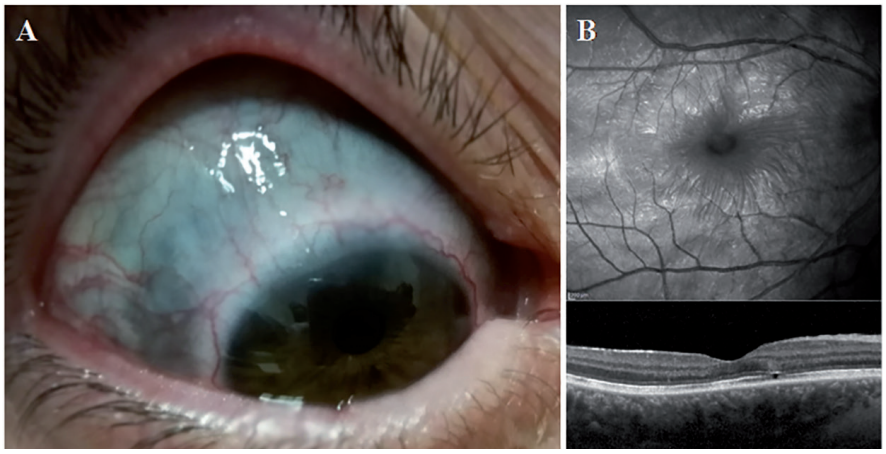

Fig. 7. A: Diffuse scleral thinning of the right eye of a patient following resolution of grade 4 active diffuse anterior scleritis associated to rheumatoid arthritis.
B: Optical coherence tomography showing epiretinal macular membrane and focal perifoveal disruption of the ellipsoid zone following resolution of exudative retinal detachment in the right eye of a patient affected by idiopathic posterior scleritis.

with our results, Doctor *et al*. reported a clinical response within an average time of 13.2 weeks in 10 patients affected by refractory scleritis and treated with infliximab (16). Similarly, Ragam *et al*. described 17 patients treated with TNF-α inhibitors with 71% of them achieving control of inflammation in a mean time of 5 months. The latter also reported a significant improvement in the inflammation grade of scleritis (8). Accordingly in our cohort the scleritis grade significantly decreased from baseline to 3 months and from baseline to the last follow-up visit suggesting both a rapid response and a sustained efficacy over time. Additionally, a significant reduction in the number of relapses was also detected.

With regard to the daily GC intake, only 5 patients continued to receive 10 mg or more of prednisone or equivalent at the last follow-up visit and the mean GC dosage was significantly reduced. Therefore, in agreement with previous reports (8, 16), a significant GC-sparing effect was observed. In the study of Ragam et al, no differences were found in the mean visual acuity. Accordingly, we did not detect any significant difference concerning BCVA, thus suggesting the ability of TNF-α inhibitors to preserve visual acuity over time. Noteworthy, this is of high relevance, since in our study 37.5% of eyes presented with more severe forms including necrotising scleritis and/or posterior scleritis.

The survival curve of our cohort affected by refractory scleritis displayed an estimated overall good drug retention rate of 58.9% and 51.6% at 12- and 36-months respectively. TNF-α blockade was associated with a low rate of AEs, thus confirming the excellent safety profile of these agents.

Scleritis was associated with a systemic disease in 16 out of 19 patients. Several authors have reported a lower remission rate when associated systemic inflammatory diseases are present (17). However, since only 3 of our patients presented with idiopathic scleritis we could not evaluate this variable from a statistical standpoint. Interestingly, all 3 of them achieved control of inflammation, without the development of any ocular complication.

Study limitations include the retrospective design, the lack of a control group and the heterogeneity of systemic and ocular involvement. Regarding ocular involvement, the inclusion of patients with the most severe entities such as necrotising scleritis and posterior scleritis might have led to an underestimation of drug effectiveness. Hence, further randomised, prospective studies with larger cohorts of patients are warranted to confirm these preliminary results and to evaluate whether biologic agents should be considered as first-line treatment, especially in the most severe cases of scleritis such as necrotising and posterior scleritis.

An expert panel has recommended anti-TNF-α therapy as a feasible option in GC-dependent scleritis patients who have failed first-line immunomodulatory therapy (18). While mild forms of scleritis respond well to treatment with oral non-steroidal anti-inflammatory drugs, more chronic and severe forms may require GC-sparing agents, both conventional and biologic response modifiers (1, 19, 20). In this regard, management of the most severe cases of scleritis may be optimised by following a top-down algorithm, in which early and aggressive treatment with biologics should be contemplated in order to attain complete control of inflammation and to prevent or minimise visual impairment. Indeed, suboptimal treatment can lead to severe anatomical and visual consequences responsible for a high disease burden due to a compromised quality of life and considerable socio-economic implications (1, 21).

In conclusion, our findings highlight the efficacy of TNF-α blockade in the treatment of scleritis with a marked control of scleral inflammation both in the short and in the long-term and a significant reduction in the number of relapses. Moreover, TNF-α inhibitors have shown to preserve visual function, to have a good safety profile and a significant GC-sparing effect.

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