ANTI-TNF-α THERAPY IN REFRACTORY UVEITIS ASSOCIATED WITH SARCOIDOSIS. MULTICENTER STUDY OF 17 PATIENTS

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Abstract

Objectives: To assess anti-TNF-α therapy response in uveitis associated with sarcoidosis refractory to conventional immunosuppressive therapy.

Methods: Open-label, multicenter, retrospective study on patients with sarcoid uveitis who underwent anti-TNF-α therapy because of inadequate response to conventional therapy including corticosteroids and at least 1 systemic synthetic immunosuppressive drug. The main outcome measurements were degree of anterior and posterior chamber inflammation, visual acuity, macular thickness and immunosuppression load.

Results: Seventeen patients (8 men; 29 affected eyes; mean±standard deviation age 38.4±16.8; range 13-76 years) were studied. Patients had bilateral hilar lymphadenopathy (58.8%), lung parenchyma involvement (47.1%), peripheral lymph nodes (41.2%) and involvement of other organs (52.9%). Angiotensin-Converting Enzyme was elevated in 58.8%. The most frequent ocular pattern was bilateral chronic relapsing panuveitis. The first biologic agent used was adalimumab in 10 (58.8 %) and infliximab in 7 (41.2%) cases. Infliximab 5 mg/kg /intravenously/every 4-8 weeks and adalimumab 40 mg/subcutaneously/every 2 weeks were the most common administration patterns. In most cases anti-TNF-α therapy was given in combination with immunosuppressive drugs. The mean duration of follow-up was 33.9±17.1 months. Significant improvement was observed following anti-TNF-α therapy: Baseline results versus results at 2 years from the onset of biologic therapy were the following: the median of cells in the ocular anterior chamber [interquartile range-IQR] 0.5 [0-2] versus 0 [0-0] (p=0.003), vitritis 0 [0-1.25] versus 0 [0-0] (p=0.008), macular thickness (391.1±58.8 versus 247±40.5 microns) (p=0.028), and visual acuity 0.60±0.33 versus 0.74±0.27; p=0.009;-The median daily [interquartile range] dose of prednisone was also

reduced from 10 [0-30] mg at the onset of the anti-TNF-α therapy to 0 [0-0] mg at 2 years (p=0.02). Significant reduction was also achieved in the immunosuppressive load.

Conclusion: Anti-TNF-α therapy is effective in sarcoid uveitis patients refractory to conventional immunosuppressive therapy. Infliximab and adalimumab allowed a substantial reduction in prednisone dose despite having failed standard therapy.

1. Introduction

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology. The most commonly involved organs are the lungs and lymph nodes, followed by skin, liver, eyes and nervous system (1-3)**.** Ophthalmologic manifestations occur in 10-80% of the cases. Any ocular structure may be affected, anterior uveitis being the most common manifestation (4-6)**.**

The pathogenesis of sarcoidosis remains unclear. Antigen presentation leads to activation of CD4 cells and differentiation to Th1 cells that secrete interleukin 2 (IL-2) and interferon gamma (IFN-γ). This also increases macrophage tumor necrosis factor alpha (TNF-α) production (1;2;7-9).

Corticosteroids are the cornerstone of the therapy in sarcoidosis (2;10;11)**,** immunosuppressive agents such as methotrexate (MTX), azathioprine (AZA) and mycophenolate are given in refractory cases (7;11;12). Several studies support the use of monoclonal antibodies against TNF-α, mainly infliximab (IFX), in the treatment of pulmonary sarcoidosis, uveitis, cutaneous sarcoidosis including lupus pernio, and neurosarcoidosis (8;13-17). However, so far evidence is based on small series or case reports.

Taken together all these considerations, our aim was to assess the clinical response to biologic therapy in a series of patients with sarcoid uveitis refractory to standard conventional synthetic immunosuppressive therapy.

2. Patients and methods

2.1. Design and Enrollment Criteria

We set up an interventional case series, open-label~~,~~ multicenter study that included 17 patients with sarcoid uveitis refractory to conventional immunosuppressive therapy.

Patients were studied at the outpatient clinics of the Uveitis Units of 12 referral centers from Spain.

The diagnosis of ocular sarcoidosis was performed according to the proposed International Criteria (18). Biopsy-supported diagnosis with a compatible uveitis was performed in 6 patients that were labeled as having definite ocular sarcoidosis. Another 7 patients met criteria for presumed ocular sarcoidosis since biopsy was not done but in all of them uveitis was associated with a chest x-ray that showed bilateral hilar lymphadenopathy. The remaining 4 patients were considered as having probable or possible sarcoidosis according to these proposed criteria (18).

Patients included in the present study also required the presence of uveitis with partial or no response to corticosteroids and at least 1 conventional immunosuppressive drug. Patients in this study were allowed to adjust topical, periocular or intraocular therapies. Before the onset of biological therapy evidence of malignancy or systemic infections, including hepatitis B or hepatitis C, was excluded. As indicated in the Spanish National Guidelines, latent tuberculosis was excluded by a tuberculin skin testing (PPD) and/or quantiferon and chest radiograph in all patients receiving anti-TNF-α drugs. Following this procedure, prophylaxis with isoniazid was initiated in 2 patients with latent tuberculosis at least 4 weeks before the onset of the biologic agent. Overall, prophylaxis with isoniazid was maintained for 9 months.

Since biologic therapy in uveitis is an off-label indication, written informed consent was requested and obtained from all patients. For the inclusion in the present study patients were required to have been followed for at least 2 years at the Uveitis Units.

Uveitis was classified anatomically according to the International Uveitis Study Group (IUSG) classification (19)**.**

2.2 Outcome Variables

Intraocular inflammation, macular thickness, visual acuity, sparing effect of corticosteroid and immunosuppression load score were the outcome variables. These outcome variables were recorded at baseline and at 1 week, 1 month, 3 months, 6 months 1 year and 2 years. They were assessed according to a follow-up protocol study agreed by all researchers that was performed in each center.

The degree of intraocular inflammation was evaluated according to "The Standardization of Uveitis Nomenclature (SUN) Working Group"(20). Vitreous haze, called vitritis, was measured by the Nussenblatt scale (21)**.**

Fluorecein angiogram (FA) was performed routinely before and after the onset of treatment to determine the presence or absence of retinal angiographic leakage. FA was reviewed for the presence or absence of vasculitis, papillitis and cystoid macular edema (CME). Retinal vasculitis was defined as retinal angiographic leakage, staining and/or occlusion on FA. Choroiditis and retinitis were considered active or inactive depending on the presence or absence of activity data on the ophthalmoscopic examination and/or FA.

Macular thickness was measured by optical coherence tomography (OCT). All the HD-OCT scans were performed using Cirrus HD-OCT (Carl Zeiss, Ca, USA). Scans were obtained using the 512x128 scan Pattern. Macular thickening was defined as a macular thickness greater than 250 μm whereas CME was defined as a macular thickness greater than 300 μm.

The best-corrected visual acuity (BCVA) was determined using the Snellen test. Snellen visual acuities were converted to logarithm of the minimum angle of resolution (logMAR) scores for statistical analysis.

The degree of immunosuppression (immunosuppression load score) was calculated according to the semiquantitative scale proposed by Nussenblatt et al (22). The grading scheme provides a combined, single numeric score for the total immunosuppression load per unit of body weight per day. Grades for each agent (prednisone, cyclosporine [CsA], AZA, MTX, and chlorambucil) ranged on a scale from 0 to 9, whereas mycophenolate mofetil ranged from 0 to 7. For patients receiving multiple medications, the sum of the grading score for each drug was used to calculate the total immunosuppression score at the baseline visit and at each visit on a scale from 0 to 15. Topical or periocular corticosteroid therapy was excluded from the calculation of the immunosuppressive load. The dose of biologic agents was not used to calculate the final immunosuppressive load.

A relapse was considered to be present if a patient that was in remission experienced a new flare of uveitis (20). Remission was defined as inactive disease for at least 3 months after discontinuation of all treatment for eye manifestations (21).

2.3. Statistical Analysis

Statistical analysis was performed using the software STATISTICA (StatSoft Inc. Tulsa, Oklahoma, USA). Results were expressed as mean± standard deviation (SD) for variables with a normal distribution, or as median [25th-75th interquartile range (IQR)] when they were not normally distributed. The comparison of continuous variables was performed using the Wilcoxon test.

The following variables were assessed: best-corrected visual acuity, anterior chamber cells, vitritis, choroiditis, retinitis, retinal vasculitis and OCT. Comparisons of these variables were made between baseline and 1st week, 1st month, 6th month, 1st year and 2nd year.

3. Results

3.1. Demographic and general data at baseline

Data from 17 patients (29 affected eyes) with uveitis associated with sarcoidosis refractory to conventional immunosuppressive therapy were reviewed **(Table 1).** Women slightly outnumbered men (9 women/ 8 men). The mean age was 38.4 ± 16.8 years (range 13-76).

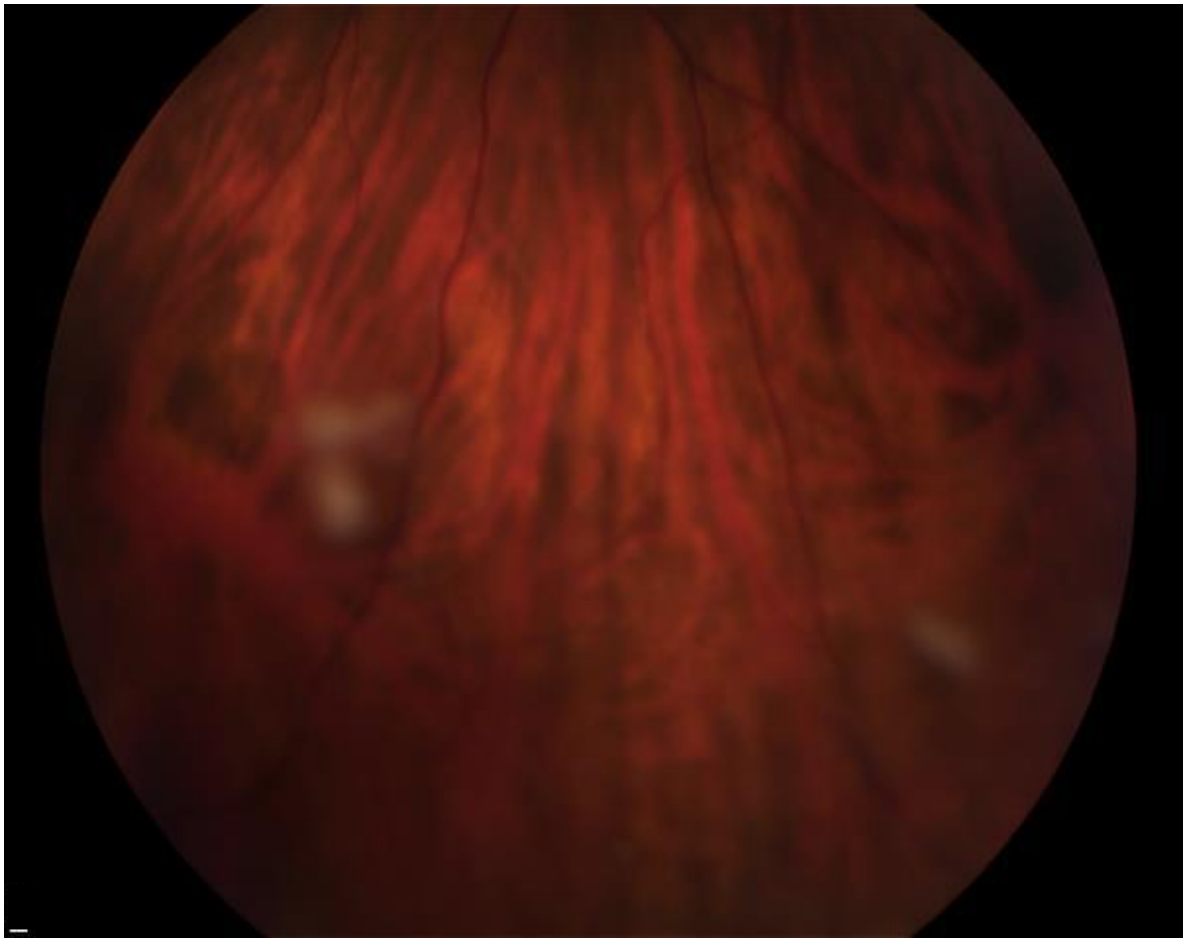
Table 1. Main epidemiological and ophthalmologic features of a series of 17 patients with sarcoidosis undergoing anti-TNF-α therapy because of uveitis refractory to conventional immunosuppressive drugs.

Number of patients	17
Mean age ± SD (years)	38.4±16.8years
Sex (men/women)	8/9
Elevated ACE	10 (58.8%)
Number of affected eyes	29
Pattern of uveitis	
Bilateral / unilateral	12/5
Anterior	3/17 (17.6%)
Posterior	1/ 17 (5.9%)
Middle	2/17 (11.8%)
Panuveitis	11/17 (64.7%)
Previous treatment:	
MTX	13/17 (76.5%)
CyA	5/17 (29.4%)
AZA	3/17 (17.6%)
Intravenous pulses of methylprednisolone	1 (5.9%)
Patients on prednisone at start of biologic therapy	12
Biologic therapy:	
First biologic drug used:	
ADA	10 (58.8%)
IFX	7 (41.2%)
Monotherapy / Combined with IS drugs*	3/14
Second biologic drug used (switching)	6

ACE: Angiotensin converting enzyme. CsA:cyclosporine A. AZA: azathioprine. MTX: methotrexate. IFX: infliximab. ADA: adalimumab.
*Conventional IS (immunosuppressive) drugs.

Extraocular manifestations of sarcoidosis were observed in most cases. The most common were bilateral hiliar adenopathy (58.8%), lung parenchyma (47.1%) and peripheral lymph nodes (41.2%). Angiotensin converting enzyme (ACE) was elevated at 58.8% of patients. In 35.3% of patients diagnosis of sarcoid uveitis was confirmed by a biopsy. All but 1 patient had extraocular manifestations of sarcoidosis. In the patient without extraocular manifestations the diagnosis of ocular sarcoidosis was made by the presence of elevated levels of ACE and typical snowballs in the vitreous **(Figure 1).**

Figure 1. Snowballs in the vitreous of a patient with sarcoidosis.



Uveitis was bilateral in most cases (70.6%), having a chronic course in 94.1% of the patients. Panuveitis was the most frequent pattern of ocular involvement (64.7%) and Mutton-fat keratic precipitates and snowballs in vitreous, the most typical findings of sarcoid uveitis, were present in 2 and 4 of the 17 patients respectively.

Only one patient rejected to take corticosteroids when ocular manifestations of sarcoidosis were diagnosed. The remaining patients were initially treated with oral corticosteroids. Besides oral corticosteroids (maximum prednisone daily dosage 60 mg/day, the mean initial dose of prednisone at the time of diagnosis of ocular sarcoidosis was 47.3±14.1 mg/day [IQR 40-60]). Also, before the onset of the biologic therapy patients had received the following drugs: Intravenous pulses of methylprednisolone that were given to 1 patient (two consecutive pulses of 500 mg/every day). CsA was used in 5 patients (mean dose 4.6±0.9 mg/kg/day). Thirteen patients received MTX (administered in most cases subcutaneously) (mean dose 19.6±3.8 mg/week) and 3 AZA (mean dose: 116.7 ± 28.9 mg/day).

3.2. Biologic therapy

In all patients the biologic therapy was prescribed because of poor control of intraocular inflammation with conventional immunosuppressive therapy. The first biologic agent used was adalimumab (ADA) in 10 (58.8%) and IFX in the remaining 7 patients (41.2%) **(Table 1)**. They were given as a monotherapy to 3 patients and in association with conventional immunosuppressive drugs (MTX [n=11], AZA [n=2], and mycophenolate mophetil [n=1]) in the remaining 14 cases.

IFX dose was 5 mg/kg/intravenously every 4 to 8 weeks; every 4 weeks (3 patients), every 6 weeks (1 patient) or every 8 weeks (3 patients). ADA regimen was 40 mg/subcutaneously every other week in all the 10 cases. In 4 cases (2 patients on IFX

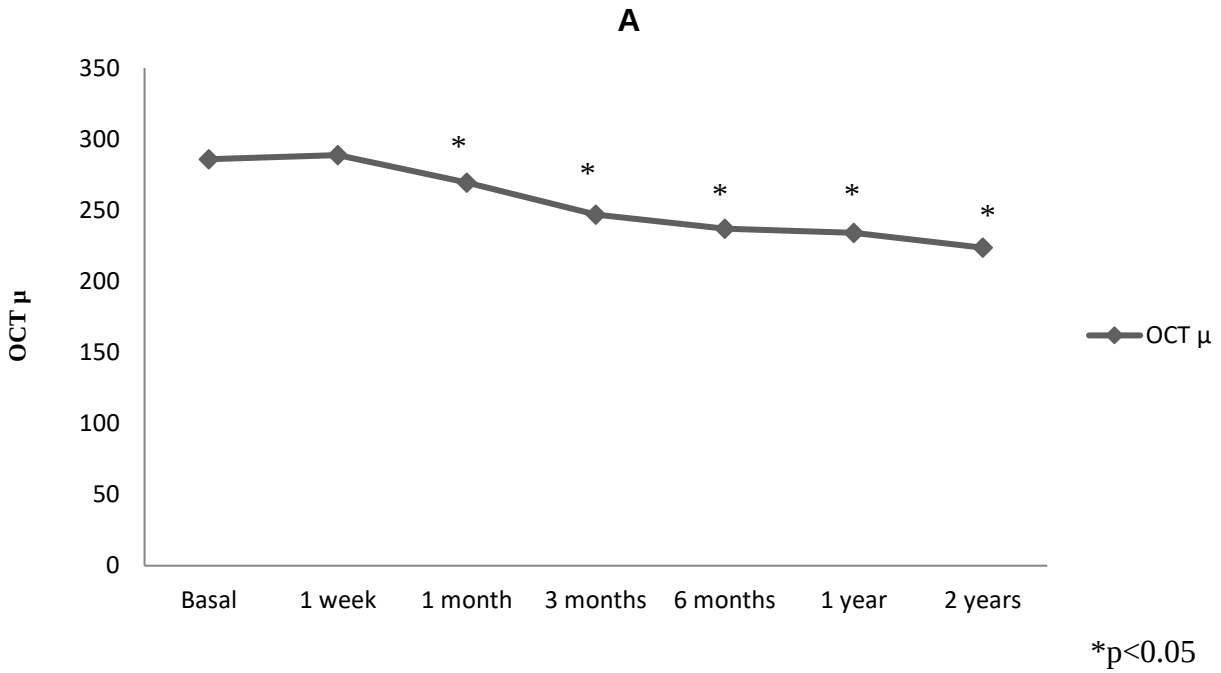
and 2 patients on ADA) the interval between doses was enlarged because of clinical improvement, and in 2 cases (1 on IFX and 1 on ADA) the intervals were shortened due to inefficacy.

All the patients were included in the study when the first biologic (anti-TNF-α) agent was used. After the first choice of biologic therapy, 2 patients were switched from IFX to ADA (one of them due to intolerance and another due to lack of response) and 2 patients were switched from ADA to IFX due to lack of adequate response. ADA was switched to golimumab (GOLI) in 1 patient due to inefficacy. IFX was also switched to GOLI in 1 patient because of dyspnea.

3.3. Clinical efficacy of anti-TNF-α drugs

Intraocular inflammation, macular thickness, visual acuity, sparing effect of corticosteroids and immunosuppression load were the outcome variables. All of them showed an improvement at 2 years after the onset of biologic therapy **(Figures 2, 3 and 4)**.

Figure 2. Rapid and maintained improvement following the onset of anti-TNF-α therapy (data expressed as mean values compared with basal results): **(A)** macular thickness and **(B)** best corrected visual acuity (BCVA). * p<0.05.



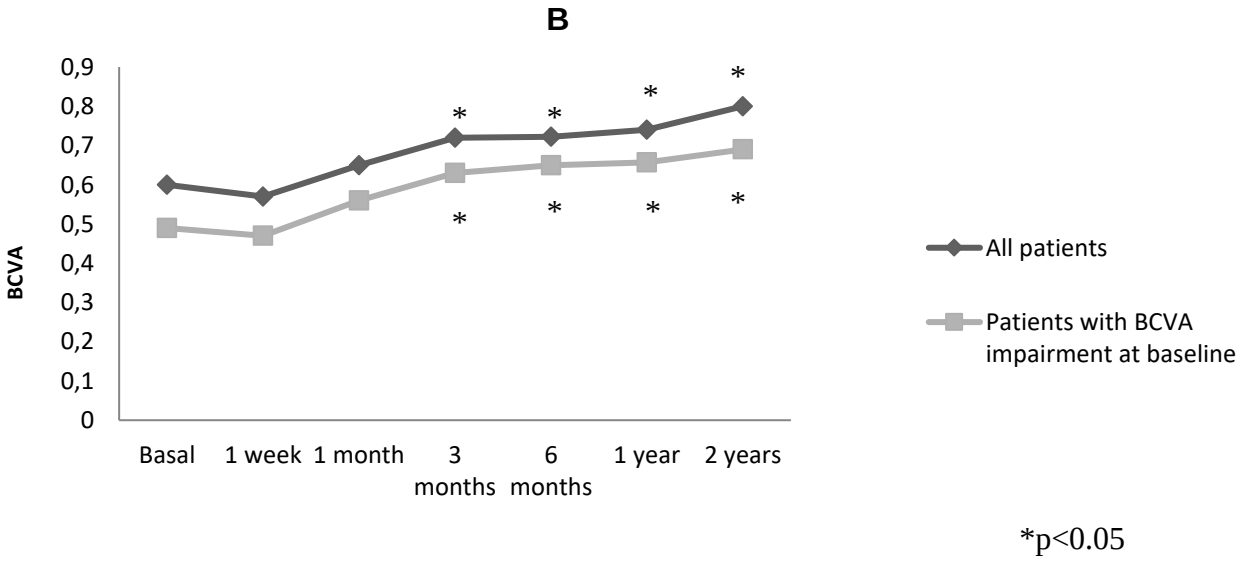


Figure 3.

Figure 3A. Cells in the ocular anterior chamber (AC cells) at the onset of anti TNF-α therapy and after two years of follow-up. Data shown in **Figure 3A** are only limited to the eyes that were affected at the onset of anti TNF-α therapy.

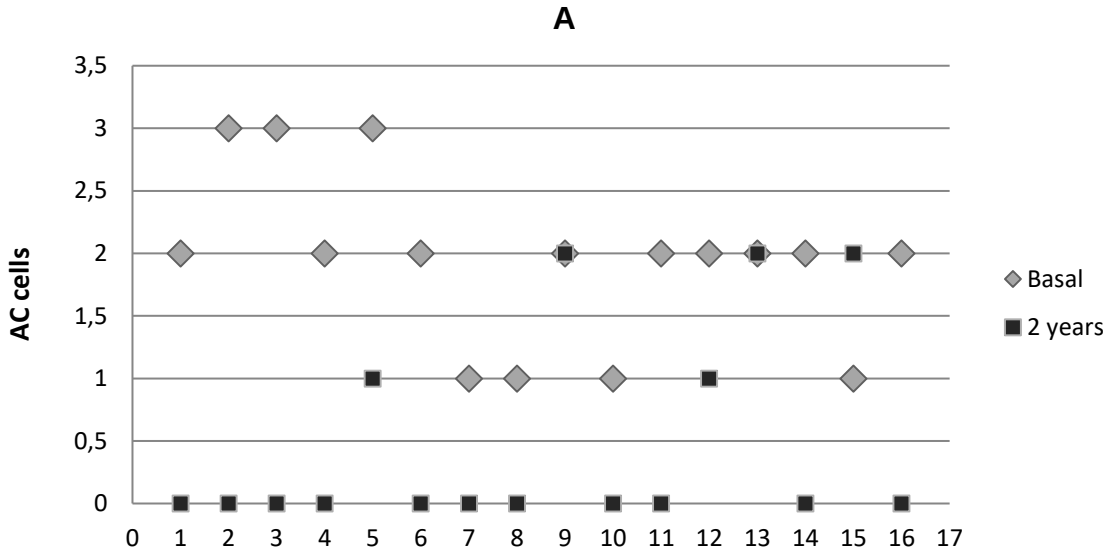


Figure 3B. Vitreous haze (vitritis) at the onset of anti TNF-α therapy and after two years of follow-up. Data shown in **Figure 3B** are only limited to the eyes that were affected at the onset of anti TNF-α therapy.

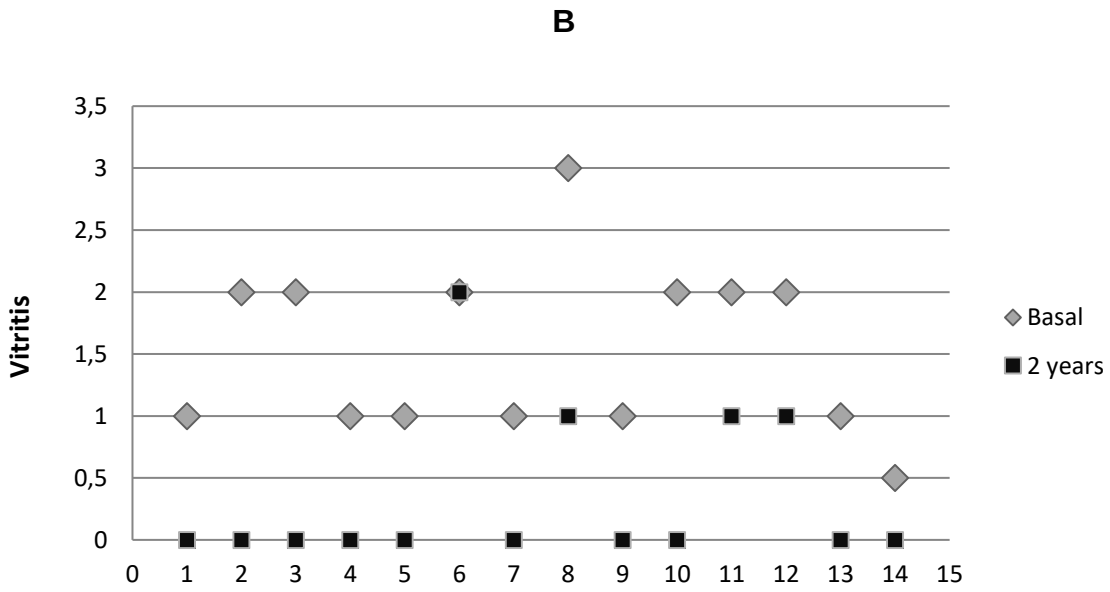


Table 2. Anti-TNF-α therapy led to improvement of active inflammation of anterior chamber cells (AC cells) and vitritis, choroiditis and retinitis and OCT values. Whenever any score of activity was present, data were expressed as percentage (%) of affected eyes in the 17 patients.

	AC cells	Vitritis	Choroiditis	Retinitis	OCT>250µ	OCT>300µ
Baseline	50%	30%	8.8%	2.9%	37.5%	20%
1 week	50%	30%	8.8%	2.9%	37.5%	20%
1 month	15.6% *	28.1%	8.8%	8.8%	37.5%	20%
6 months	3.12% *	12.5% *	2.9%	2.9%	18.7% *	5.9% *
1 year	12.5% *	18.7% *	2.9%	2.9%	12.5% *	0.5% *
2 years	21% *	9.4% *	0%	0%	3.1% *	0% *

Active ocular inflammation was considered if one of the following features was present: AC cells 0.5-4+, vitritis 1-4+ (according to the Nussenblatt scale) (22), choroiditis, retinitis, or OCT >250 microns.

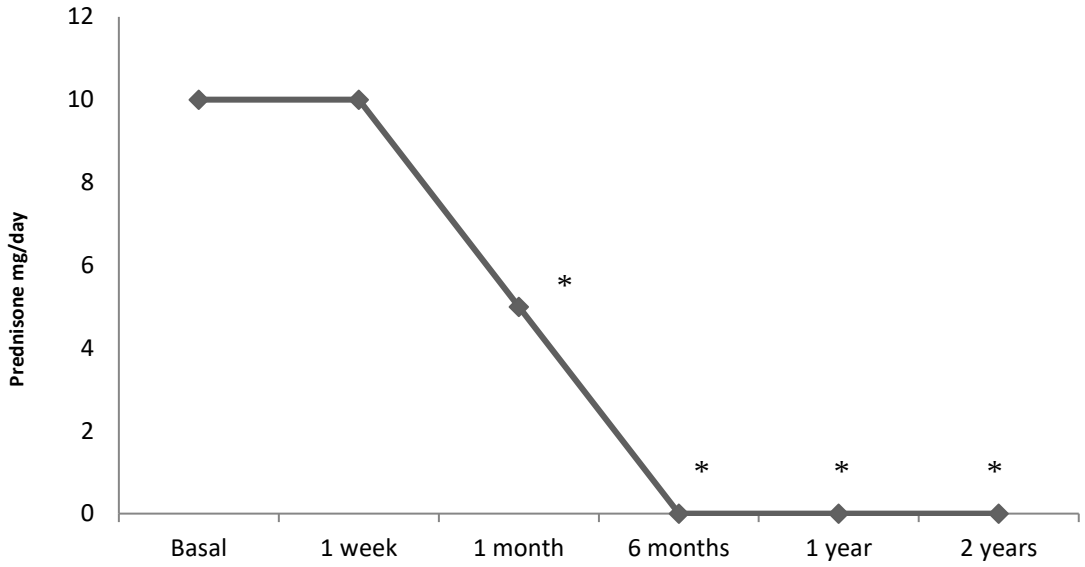
*p<0.05

With respect to this, when compared with finding observed at the onset of anti-TNF-α therapy, at month 1 the number of anterior cell showed a statistically significant reduction **(Table 2)**. Significant reduction of vitritis was also observed at month 6 **(Table 2)**. At 1 year the significant reduction of anterior chamber cells (from a median [IQR] of 0.5 [0-2] at the onset of biologic therapy to 0 [0-0] at 1 year (p<0.01) and vitritis (from a median [IQR] of 0 [0-1.25] at the onset of biologic therapy to 0 [0-0] at 1 year (p<0.01)) was maintained. This significant reduction in anterior cells and vitritis was also observed at 2 years after the onset of anti-TNF-α therapy **(Figures 3A, 3B)** In addition, the number of patients with active choroiditis decreased from 2 patients (3 of 34 eyes [8.8%]) at the onset of biologic therapy to 0 patients at 2 years. Active retinitis

that was present in 1 patient (1 of 34 eyes [2.9%]) at the onset of the biologic therapy was not clinically evident in any of the 17 patients after 2 years from the onset of biologic therapy **(Table 2)**. At the onset of biologic therapy 8 patients (13 of 34 eyes) had macular thickening (OCT>250μ) and 7 had CME (OCT>300μ). At month 6 the percentage of eyes with OCT values >250 and >300 showed a statistically significant reduction **(Table 2)**. OCT improvement was also observed 2 years after the onset of biologic therapy **(Table 2)**. The number of patients with retinal vasculitis decreased from 5 patients (5 of 34 eyes) to 0 patients at 2 years. Macular thickness was reduced from 391.1±58.8 microns to 247±40.5 microns at 2 years (p=0.03). Moreover, the mean BCVA increased from a mean± SD value of 0.6±0.33 at the onset of the biologic therapy to 0.74±0.27 at 2 years after the onset of the biologic therapy (p<0.01). Sparing effect on corticosteroid dose and reduction of the immunosuppressive load was also observed at 2 years **(Figures 4A and 4B)**.

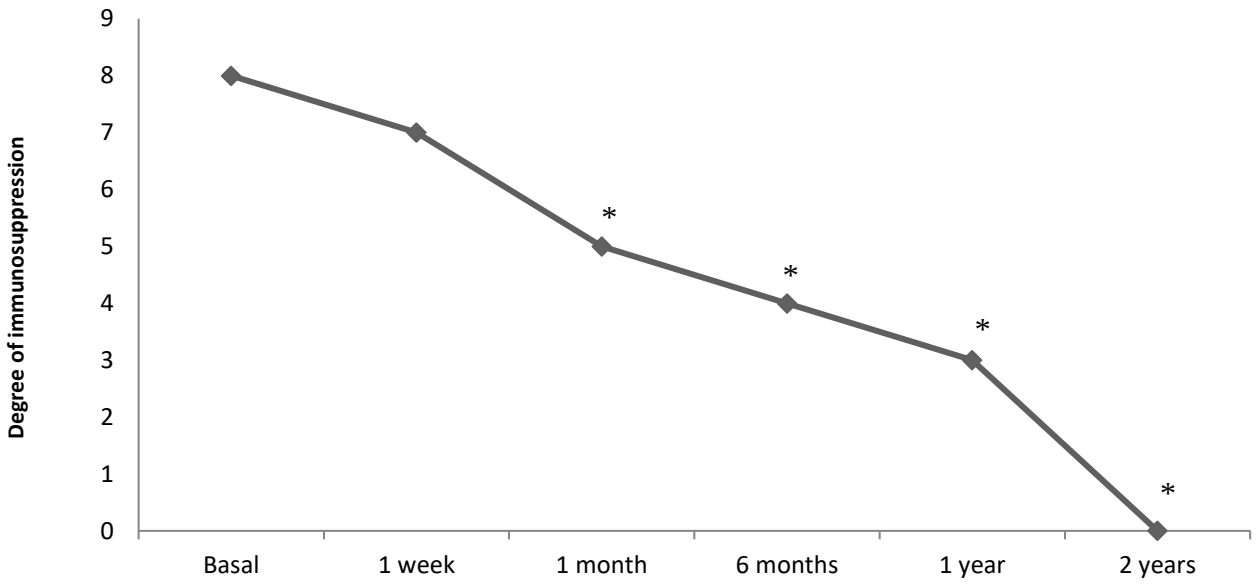
Figure 4. Sparing effect following anti-TNF-α therapy on: **(A)** Corticosteroid dose (values expressed as median of prednisone/day) and **(B)** Immunosuppression load score (values expressed as median of score). * p<0.05.

A



*p<0.05

B



*p<0.05

In this regard, at the onset of the biologic therapy the daily median [IQR] dose of prednisone was 10 [0-30] mg. The daily dose of prednisone had been significantly reduced after 2 years from the onset of anti-TNF-α therapy 0 [0-0] mg (p= 0.02). In addition, the median [IQR] immunosuppression load score had been successfully

reduced from 8 [4.5-11] to 0 [0-1] after 2 years from the onset of the biologic therapy; $p<0.01$ **(Figure 4B)**.

Following prednisone tapering 4 (3 of them undergoing ADA and 1 IFX therapy) of 12 patients who were taking corticosteroids at the onset of the biologic therapy had a new flare of intraocular inflammation that resolved with topical treatment in 3 cases and increasing the dose of prednisone in the other case (who was receiving ADA at the time of the flare). None of these patients experienced additional flares of the disease. No flares of the disease were observed in the remaining 8 patients who were taking corticosteroids when the biologic therapy was started. None of the patients had non ocular flares of sarcoidosis during prednisone reduction while they were on biologics.

3.4. Follow-up and side-effects

Although all the patients were followed for at least 2 years after the onset of biologic therapy, 2 of them did not complete two years of anti-TNF-α treatment. The mean duration of follow-up after the onset of anti TNF-α therapy was 33.9 ±17.1 months.

At 2 years complete ocular clinical control of inflammation had been achieved in 14 (82.3%) of 17 patients. With respect to this, only 1 (5.8%) of the 17 patients did not experience clinical improvement. This patient was with ADA. The other 2 patients (one treated with ADA and another with IFX) achieved an improvement in all ocular parameters except for OCT. Because of clinical improvement, the biologic therapy was discontinued in 2 ADA-treated patients.

Biologic therapy was well tolerated in most patients during the follow-up. The most common complications were minor side effects, mainly mild infusion reactions to IFX and local reaction at the site of ADA injection (pain and erythema). However, none of the patients who suffered infusion reactions or local reaction at the site of administration

of the biologic agent required discontinuation of the anti-TNF-α therapy. Severe complications that led to discontinuation of these biologic agents were observed in 2 patients (psoriasis while being on ADA in 1 patient and dyspnea following IFX administration in the other)**.**

4. Discussion

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology. Ocular manifestations were found in 11.8% of patients included in the Case Control Etiologic Study of Sarcoidosis (ACCESS) that enrolled 736 patients with sarcoidosis within 6 months of diagnosis from 10 clinical centers in the United States (23). They were more common in women and in African-American individuals (23). However, according to other series (5)**,** up to 80% of patients with sarcoidosis may have ocular manifestations. Any ocular structure may be potentially affected in sarcoidosis (5;24;25)**,** being uveitis the most common manifestation (4-6)**,** mainly anterior uveitis (6). Posterior segment involvement occurs in about 25% of patients and it may be associated with neurological manifestations (4;10). Panuveitis is observed in up to 33% of patients (25). Complications leading to visual loss, such as cystoid macular edema, cataracts, secondary glaucoma, vitreous opacities and retinal scars, are more commonly observed in posterior uveitis and panuveitis associated with sarcoidosis (24-26)**.**

Corticosteroids are the cornerstone of the therapy in sarcoidosis. Topical administration is used for anterior uveitis (2;10;11). Intraocular or systemic corticosteroids are preferred as the initial treatment for intermediate, posterior or panuveitis. Nevertheless, in corticosteroid-refractory patients or when severe side effects appear, immunosuppressive agents are usually prescribed, being MTX, AZA and cyclophosphamide the most commonly used (8;11)**.**

Several case reports and some case series and a randomized trial (7) assessing the efficacy of TNF-α antagonists in refractory sarcoidosis have been published. These biologic agents have been reported to be useful for the treatment of pulmonary and extrapulmonary sarcoidosis, being IFX the most extensively studied (3;8;13-17;27-29). However, information on anti-TNF-α therapy in sarcoid-related uveitis is scarce. In this regard, a few patients with ocular manifestations who responded favourably to IFX were included in a controlled trial on the effect of this biologic agent in extrapulmonary sarcoidosis (15). Patients with uveitis treated with IFX have also been included in series of patients with refractory sarcoidosis (16;30). However, to the best of our knowledge, there are no clinical studies addressing specifically the effect of IFX in ocular sarcoidosis.

In line with the above, some cases of sarcoid uveitis were included in series of IFX-treated chronic non-infectious uveitis (31;32). In this regard, a prospective trial showed good rates of retention in a 2-year follow-up study (33;34). *Baughman* et al. reported seven patients with sarcoidosis that experienced marked improvement of ocular inflammation following IFX therapy (35)**.** Two patients with refractory retinal vasculitis due to sarcoidosis also showed excellent response to IFX (36).

ADA also yielded good results in cases of ocular sarcoidosis included in series of patients with refractory uveitis (37;38)**.** Interestingly, *Erckens* et al (39) reported successful response to this monoclonal antibody in a prospective study on twenty-six sarcoidosis patients with refractory chronic posterior uveitis.

TNF-α is implicated in adaptative responses of the immune system (40). This proinflammatory cytokine has also been implicated in the pathogenesis of uveitis as high concentrations of TNF-α have been found in the aqueous humor or serum of some

patients with uveitis (41)**.** In addition, intravitreal injection of TNF-α induces uveitis in rabbits (42;43)**.**

Until 2014 there were 5 five marketed anti TNF-α drugs in Spain: the soluble fusion protein of TNF-α type II receptor (etanercept), and the monoclonal antibodies against TNF-α (IFX, ADA, certolizumab and GOLI). Etanercept, a TNF-α p75 soluble receptor fusion protein, failed to show benefit in patients with refractory ocular sarcoidosis (44), as well as in a randomized controlled trial of uveitis associated with juvenile-idiopathic arthritis (45)**.**

GOLI is a fully human monoclonal IgG1 antibody specific for TNF-α that is administered subcutaneously once a month. Some reports have shown its efficacy in refractory cases of juvenile idiopathic arthritis related uveitis, Behçet´s disease related uveitis and uveitis related with spondyloarthropaties (46;47)**.** In these cases it was used after inadequate response or intolerance to other TNF α inhibitors. Certolizumab is a pegylated humanized antibody Fab fragment of a monoclonal antibody specifically directed against TNF-α, which binds the soluble and the cell bound forms. In the past year, several studies have described the beneficial effect of certolizumab in the management of noninfectious uveitis refractory to conventional immunosuppressive therapy and to other anti TNF agents (48;49).

IFX is a chimeric monoclonal antibody that inactivates the pro-inflammatory cytokine TNF-α. ADA is a fully human monoclonal IgG1 antibody also specific for TNF-α, which is administered subcutaneously. Both IFX and ADA have proved to be effective in the management of refractory immune mediated uveitis (50)**.**

Most patients with refractory uveitis require high doses of IFX (generally 5 mg/kg/intravenously) to achieve control of intraocular inflammation and avoid visual loss. In keeping with former studies on IFX treated patient with uveitis (31;51), all our

patients with sarcoid uveitis were treated with 5 mg/kg/ intravenously at 0, 2, 6 weeks, and then they continued with a maintenance dose every 4 to 8 weeks. ADA was given subcutaneously at a dosage of 40 mg every other week.

In our series dose adjustment, either shortening or prolonging the interval between administrations, was required in cases with persistent active uveitis or with adequate control of inflammation, respectively. During follow-up, some patients were switched to a second biologic agent. It was due to insufficient response, either because of lack or loss of efficacy or due to adverse events. In keeping with our findings, previous studies have reported good responses after switching TNF-α inhibitors (52-54). However, to the best of our knowledge, there were no previous reports showing efficacy of GOLI in refractory sarcoid uveitis.

In keeping with former studies (38;39;51), we found a corticosteroid sparing effect following TNF-α therapy **(Figure 4A)**.

In our series, two patients who were on ADA were discontinued after being 23 and 9 months in remission, respectively. In this regard, some authors have proposed discontinuation of the biologic therapy in patients with persistently inactive ocular inflammation: However, it remains unclear how long anti TNF-α therapy should be continued in responding patients (32;37;55;56). With respect to this, relapses are not uncommon following discontinuation of the biologic therapy (57). Therefore, close follow-up should be performed to patients in whom these agents are discontinued.

Potential adverse effects of anti TNF-α agents include reactivation of tuberculosis, opportunistic infection, central demyelination and malignancies(41;58). In our series two patients had to discontinue the biologic therapy due to side effects, one of them because of dyspnea and the other because of development of psoriasis. Paradoxically,

TNF-α inhibitors have been reported to cause uveitis (59-61), sarcoid-like reactions including sarcoid-related uveitis (61-64) and psoriasiform skin disease .

5. Conclusion

Anti-TNF- α therapy is effective and relatively safe in refractory uveitis due to sarcoidosis. Anti-TNF- α drugs yield a corticosteroid-sparing effect in patients with sarcoid uveitis.

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7. Conflict of interest statement

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9. References

(1) Hamzeh N. Sarcoidosis. Med Clin North Am 2011; 95(6):1223-1234.

(2) Culver DA. Sarcoidosis. Immunol Allergy Clin North Am 2012; 32(4):487-511.

(3) Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet 2014; 383(9923):1155-1167.

(4) Phillips YL, Eggenberger ER. Neuro-ophthalmic sarcoidosis. Curr Opin Ophthalmol 2010; 21(6):423-429.

(5) Bonfioli AA, Orefice F. Sarcoidosis. Semin Ophthalmol 2005; 20(3):177-182.

(6) Umur KA, Tayfun B, Oguzhan O. Different ophthalmologic manifestations of sarcoidosis. Curr Opin Ophthalmol 2012; 23(6):477-484.

(7) Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357(21):2153-2165.

(8) Riancho-Zarrabeitia L, Delgado-Alvarado M, Riancho J, Oterino A, Sedano MJ, Rueda-Gotor J et al. Anti-TNF-alpha therapy in the management of severe neurosarcoidosis: a report of five cases from a single centre and literature review. Clin Exp Rheumatol 2013.

(9) Lazarus A. Sarcoidosis: epidemiology, etiology, pathogenesis, and genetics. Dis Mon 2009; 55(11):649-660.

(10) Holmes J, Lazarus A. Sarcoidosis: extrathoracic manifestations. Dis Mon 2009; 55(11):675-692.

(11) Baughman RP, Costabel U, du Bois RM. Treatment of sarcoidosis. Clin Chest Med 2008; 29(3):533-53x.

(12) Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet 2014; 383(9923):1155-1167.

(13) Pereira J, Anderson NE, McAuley D, Bergin P, Kilfoyle D, Fink J. Medically refractory neurosarcoidosis treated with infliximab. Intern Med J 2011; 41(4):354-357.

(14) Cottin V. Update on bioagent therapy in sarcoidosis. F1000 Med Rep 2010; 2.

(15) Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. Eur Respir J 2008; 31(6):1189-1196.

(16) Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. Chest 2005; 127(3):1064-1071.

(17) Sodhi M, Pearson K, White ES, Culver DA. Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis. Respir Med 2009; 103(2):268-273.

(18) Herbort CP, Rao NA, Mochizuki M. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop On Ocular Sarcoidosis (IWOS). Ocul Immunol Inflamm 2009; 17(3):160-169.

(19) Deschenes J, Murray PI, Rao NA, Nussenblatt RB. International Uveitis Study Group (IUSG): clinical classification of uveitis. Ocul Immunol Inflamm 2008; 16(1):1-2.

(20) Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005; 140(3):509-516.

(21) Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1985; 92(4):467-471.

(22) Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF, Letko E et al. Initial evaluation of subcutaneous daclizumab treatments for noninfectious uveitis: a multicenter noncomparative interventional case series. Ophthalmology 2005; 112(5):764-770.

(23) Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H, Jr, Bresnitz EA et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164(10 Pt 1):1885-1889.

(24) Rose AS, Tielker MA, Knox KS. Hepatic, ocular, and cutaneous sarcoidosis. Clin Chest Med 2008; 29(3):509-24, ix.

(25) Jabs DA, Johns CJ. Ocular involvement in chronic sarcoidosis. Am J Ophthalmol 1986; 102(3):297-301.

(26) Pan J, Kapur M, McCallum R. Noninfectious immune-mediated uveitis and ocular inflammation. Curr Allergy Asthma Rep 2014; 14(1):409.

(27) Bejerano C, Blanco R, Gonzalez-Vela C, Aguero R, Carril JM, Gonzalez-Gay MA. Refractory polymyalgia rheumatica as presenting manifestation of large-vessel vasculitis associated to sarcoidosis. Successful response to adalimumab. Clin Exp Rheumatol 2012; 30(1 Suppl 70):S94-S97.

(28) Callejas-Rubio JL, Ortego-Centeno N, Lopez-Perez L, Benticuaga MN. Treatment of therapy-resistant sarcoidosis with adalimumab. Clin Rheumatol 2006; 25(4):596-597.

(29) Kamphuis LS, Lam-Tse WK, Dik WA, van Daele PL, van Biezen P, Kwekkeboom DJ et al. Efficacy of adalimumab in chronically active and

symptomatic patients with sarcoidosis. Am J Respir Crit Care Med 2011; 184(10):1214-1216.

(30) Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respir Med 2006; 100(11):2053-2059.

(31) Benitez-Del-Castillo JM, Martinez-de-la-Casa JM, Pato-Cour E, Mendez-Fernandez R, Lopez-Abad C, Matilla M et al. Long-term treatment of refractory posterior uveitis with anti-TNFalpha (infliximab). Eye (Lond) 2005; 19(8):841-845.

(32) Lindstedt EW, Baarsma GS, Kuijpers RW, van Hagen PM. Anti-TNF-alpha therapy for sight threatening uveitis. Br J Ophthalmol 2005; 89(5):533-536.

(33) Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD et al. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol 2005; 123(7):903-912.

(34) Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS, Kurz DE et al. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Arch Ophthalmol 2009; 127(6):819-822.

(35) Baughman RP, Bradley DA, Lower EE. Infliximab in chronic ocular inflammation. Int J Clin Pharmacol Ther 2005; 43(1):7-11.

(36) Cruz BA, Reis DD, Araujo CA. Refractory retinal vasculitis due to sarcoidosis successfully treated with infliximab. Rheumatol Int 2007; 27(12):1181-1183.

(37) Suhler EB, Lowder CY, Goldstein DA, Giles T, Lauer AK, Kurz PA et al. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. Br J Ophthalmol 2013; 97(4):481-486.

(38) Diaz-Llopis M, Salom D, Garcia-de-Vicuna C, Cordero-Coma M, Ortega G, Ortego N et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology 2012; 119(8):1575-1581.

(39) Erckens RJ, Mostard RL, Wijnen PA, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. Graefes Arch Clin Exp Ophthalmol 2012; 250(5):713-720.

(40) Sanchez-Cano D, Callejas-Rubio JL, Ruiz-Villaverde R, Rios-Fernandez R, Ortego-Centeno N. Off-label uses of anti-TNF therapy in three frequent disorders: Behcet's disease, sarcoidosis, and noninfectious uveitis. Mediators Inflamm 2013; 2013:286857.

(41) Theodossiadis PG, Markomichelakis NN, Sfikakis PP. Tumor necrosis factor antagonists: preliminary evidence for an emerging approach in the treatment of ocular inflammation. Retina 2007; 27(4):399-413.

(42) Fleisher LN, Ferrell JB, McGahan MC. Ocular inflammatory effects of intravitreally injected tumor necrosis factor-alpha and endotoxin. Inflammation 1990; 14(3):325-335.

(43) Rosenbaum JT, Howes EL, Jr., Rubin RM, Samples JR. Ocular inflammatory effects of intravitreally-injected tumor necrosis factor. Am J Pathol 1988; 133(1):47-53.

(44) Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest 2005; 128(2):1062-47.

(45) Smith JA, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum 2005; 53(1):18-23.

(46) Pasadhika S, Rosenbaum JT. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. Biologics 2014; 8:67-81.

(47) Miserocchi E, Modorati G, Pontikaki I, Meroni PL, Gerloni V. Long-term Treatment with Golimumab for Severe Uveitis. Ocul Immunol Inflamm 2013.

(48) Maiz Alonso O, Blanco Esteban AC, Egües Dubuc CA, Martinez Zabalegui D.Effectiveness of certolizumab pegol in chronic anterior uveitis associated to Crohn's disease and ankylosing spondylitis. Reumatol Clin. 2014 Dec 30.

(49) Llorenç V, Mesquida M, Sainz de la Maza M, Blanco R, Calvo V, Maíz O, Blanco A, de Dios-Jiménez de Aberásturi JR, Adán A. Certolizumab Pegol, a New Anti-TNF-α in the Armamentarium against Ocular Inflammation. Ocul Immunol Inflamm. 2014 Oct 17:1-6.

(50) He Y, Jia SB, Zhang W, Shi JM. New options for uveitis treatment. Int J Ophthalmol 2013; 6(5):702-707.

(51) Sobrin L, Kim EC, Christen W, Papadaki T, Letko E, Foster CS. Infliximab therapy for the treatment of refractory ocular inflammatory disease. Arch Ophthalmol 2007; 125(7):895-900.

(52) Dhingra N, Morgan J, Dick AD. Switching biologic agents for uveitis. Eye (Lond) 2009; 23(9):1868-1870.

(53) Olivieri I, Leccese P, D'Angelo S, Padula A, Nigro A, Palazzi C et al. Efficacy of adalimumab in patients with Behcet's disease unsuccessfully treated with infliximab. Clin Exp Rheumatol 2011; 29(4 Suppl 67):S54-S57.

(54) Baughman RP, Bradley DA, Lower EE. Infliximab in chronic ocular inflammation. Int J Clin Pharmacol Ther 2005; 43(1):7-11.

(55) Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du BR et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 2006; 174(7):795-802.

(56) Baughman RP, Lower EE, Drent M. Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. Sarcoidosis Vasc Diffuse Lung Dis 2008; 25(2):76-89.

(57) Adan A, Hernandez V, Ortiz S, Molina JJ, Pelegrin L, Espinosa G et al. Effects of infliximab in the treatment of refractory posterior uveitis of Behcet's disease after withdrawal of infusions. Int Ophthalmol 2010; 30(5):577-581.

(58) Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006; 295(19):2275-2285.

(59) Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum 2007; 56(10):3248-3252.

(60) Wendling D, Paccou J, Berthelot JM, Flipo RM, Guillaume-Czitrom S, Prati C et al. New onset of uveitis during anti-tumor necrosis factor treatment for rheumatic diseases. Semin Arthritis Rheum 2011; 41(3):503-510.

(61) Hashkes PJ, Shajrawi I. Sarcoid-related uveitis occurring during etanercept therapy. Clin Exp Rheumatol 2003; 21(5):645-646.

(62) Tong D, Manolios N, Howe G, Spencer D. New onset sarcoid-like granulomatosis developing during anti-TNF therapy: an under-recognised complication. Intern Med J 2012; 42(1):89-94.

(63) Gonzalez-Lopez MA, Blanco R, Gonzalez-Vela MC, Fernandez-Llaca H, Rodriguez-Valverde V. Development of sarcoidosis during etanercept therapy. Arthritis Rheum 2006; 55(5):817-820.

(64) Dragnev D, Barr D, Kulshrestha M, Shanmugalingam S. Sarcoid panuveitis associated with etanercept treatment, resolving with adalimumab. BMJ Case Rep 2013; 2013.