Tocilizumab in uveitis refractory to other biologic drugs: a study of 3 cases and a literature review

V. Calvo-Río[1], D. de la Hera[2], E. Beltrán-Catalán[3], R. Blanco[1], M. Hernández[4], L. Martínez-Costa[5], J. Loricera[1], J. Cañal[2], J. Ventosa[2], F. Ortiz-Sanjuán[1], T. Pina[1], M.C. González-Vela[6], P. Rodríguez-Cundín[7], M.A. González-Gay[1]

[1]Divisions of Rheumatology, [2]Ophthalmology, [6]Pathology, and [7]Preventive Medicine, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; [3]Divisions of Rheumatology, and [4]Ophthalmology, Hospital General Universitario de Valencia, Spain; [5]Division of Ophthalmology, Hospital Universitario Doctor Peset de Valencia, Spain.

*Vanesa Calvo-Río, MD**
*David de la Hera, MD**
*Emma Beltrán-Catalán, MD**
*Ricardo Blanco, MD, PhD**
Marisa Hernández, MD
Lucía Martínez-Costa, MD, PhD
Javier Loricera, MD
Joaquín Cañal, MD PhD
Juan Ventosa, MD
Francisco Ortiz-Sanjuán, MD
Trinitario Pina, MD
M. Carmen González-Vela, MD, PhD
Paz Rodríguez-Cundín, MD, PhD
Miguel A. González-Gay, MD, PhD

**Drs Calvo-Río, de la Hera, Beltrán-Catalán and Blanco contributed equally to this work and share first authorship.*

Please address correspondence to: Miguel A. González-Gay, MD, PhD or Ricardo Blanco, MD, PhD, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, Avda. Valdecilla s/n., 39008 Santander, Spain.
E-mail: miguelaggay@hotmail.com
rblanco@humv.es

Received on January 4, 2014; accepted in revised form on February 18, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 84): S54-S57.

Key words: uveitis, immune-mediated diseases, anti-TNF-α agent, Behçet, tocilizumab

Funding: this work was partially supported by RETICS Programs, RD08/0075 (RIER) and RD12/0009/0013 from "Instituto de Salud Carlos III" (ISCIII) (Spain).

Competing interests: none declared.

ABSTRACT

Objective. *To evaluate the clinical response to Tocilizumab (TCZ) in three patients with non-infectious uveitis refractory to anti-TNF-α drugs.*

Methods. *Assessment of TCZ-treated patients with immune-mediated uveitis from two Spanish medical referral centres. Uveitis had been refractory to previous standard synthetic immunosuppressive drugs and at least one TNF-α inhibitor. A literature review of patients with immune-mediated uveitis treated with TCZ therapy was also conducted.*

Results. *3 women (5 eyes) with uveitis refractory to conventional immunosuppressive therapy and at least one anti-TNF-α drug were treated with TCZ. The mean age of the patients was 48.6±16.1 (range 37-67) years. In two cases uveitis was bilateral and in the other unilateral. The underlying diseases were rheumatoid arthritis in one case and Behçet's disease in the other two cases. After a mean follow-up of 7.3±5.7 (range 1–12) months using TCZ therapy, all patients experienced ocular improvement. Also, in 3 eyes inactive intraocular inflammation was achieved. None of the patients had side effects during the period of treatment with this drug. A literature review disclosed that our observations are in keeping with other reports that showed good response to TCZ in 11 of 12 patients with immune-mediated uveitis refractory to other biologic agents.*

Conclusion. *TCZ appears to be an effective and safe therapy for the management of patients with uveitis refractory to other biologic drugs.*

Uveitis encompasses different clinical syndromes characterised by an intraocular inflammatory disease that may lead to blindness (1-3).

The etiology of non-infectious uveitis is often unknown. However, it may be the result of a wide spectrum of conditions including autoimmune diseases, such as spondyloarthropathies, Behçet's disease or sarcoidosis. Treatment of patients with immune-mediated uveitis has evolved significantly in recent years. The use of off-label biological drugs, mainly monoclonal antibodies against TNF-α, for the treatment of refractory uveitis has led to important improvement in the outcome of these patients. Anti-TNF-α therapy reduces intraocular inflammation and consequently the percentage of severe sequelae and blindness (2-6). Regrettably, despite anti-TNF-α drug use in some case uveitis may persist active. Also, sometimes anti TNF-α therapy has to be discontinued because of side effects. Therefore, new therapeutic alternatives are still needed.

Interleukin-6 (IL-6) is elevated in the vitreous of patients with active intermediate and posterior uveitis (7). Tocilizumab (TCZ) is a new humanised monoclonal antibody against the interleukin-6 receptor (IL-6R), which has been approved for the treatment of rheumatoid arthritis, systemic and polyarticular juvenile idiopathic arthritis, and Castleman's disease (8).

Recent studies have demonstrated the efficacy of tocilizumab as off-label therapy for autoimmune and inflammatory diseases (9). In this regard, anti-interleukin 6 receptor (anti-IL-6R) antibodies have been proved to be effective in experimental models of autoimmune arthritis, encephalomyelitis, and also in cases of uveitis (10, 11).

Taking into account all these considerations, in the present study we aimed to evaluate the clinical response to TCZ in patients with non-infectious uveitis refractory to anti-TNF-α drugs. In addition, a literature review was also conducted.

Patients and methods

Assessment of TCZ-treated patients with immune-mediated uveitis from three Spanish medical referral centres. Uveitis had been refractory to previous standard synthetic immunosuppressive drugs and at least one TNF-α inhibitor.

As previously described (2), patients were defined as having refractory uveitis when it was not in remission despite receiving anti-TNF-α drugs or the use of these drugs was not sufficient to maintain the disease under control.

Before TCZ onset, evidence of malignancy or systemic infections, including hepatitis B or hepatitis C, was excluded. As indicated in the Spanish National Guidelines, in all patients receiving anti-TNF-α drugs, latent tuberculosis was excluded by a tuberculin skin testing (PPD) and/or quantiferon and chest radiograph. Following this procedure, in patients with latent tuberculosis prophylaxis with isoniazid is initiated at least 4 weeks before the onset of the biologic agent. Overall, prophylaxis with isoniazid is maintained for 9 months.

Uveitis was classified anatomically according to the International Uveitis Study Group (IUSG) classification (12).

TCZ was given intravenously at the dose of 8 mg/kg, every 4 weeks. Since TCZ is an off-label indication in uveitis, written informed consent was requested and obtained from all patients.

Results

Three patients (5 affected eyes) with uveitis refractory to conventional immunosuppressive therapy and at least one anti-TNF-α drug were studied. The main demographic and therapeutic data are described in Table I. All of them were women. The mean age of the patients was 48.6±16.1 (range 37–67) years. In two cases uveitis was bilateral and in the other case unilateral.

The underlying diseases were rheumatoid arthritis in one case and Behçet's disease in the other two cases.

Besides oral corticosteroids (maximum prednisone daily dosage 60 mg/day: mean±SD 55±7.1 mg/day) and before the onset of the first biologic agent, patients were treated with intraocular corticosteroids (2 patients), bolus of intravenous methylprednisolone (3 patients), methotrexate (MTX) (3 patients), cyclosporine A (CsA) (3 patients) and azathioprine (AZA) (1 patient).

Anti-TNF-α drugs were the first-choice biologic therapy in all 3 cases. In one of them infliximab (IFX) at the standard doses of 5 mg/kg at 0, 2, 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks, and in the other two adalimumab (ADA) 40 mg/subcutaneously every other week. In all of them anti-TNF-α drugs were administered in combination with conventional immunosuppressive therapy (two patients with MTX and one with CsA).

One of the patients (case 1 from Table I) with panuveitis associated with rheumatoid arthritis had been on IFX therapy for 17 months. IFX was switched to ADA because of a severe infusional reaction. Despite treatment with ADA combined with MTX and CsA during a 35-month period, the patient experienced new episodes of reactivation of uveitis. Because of that, ADA was discontinues and TCZ therapy in combination with MTX was started.

One of the two patients with uveitis associated with Behçet's disease (case 2 from Table I), ADA combined with MTX had been started because uveitis was refractory to previous synthetic immunosuppressive therapy. After 6 years on treatment with ADA the patient suffered new episodes of reactivation of intraocular inflammation so ADA was switched to golimumab (50 mg/subcutaneously every 4 weeks) combined with MTX. Regrettably, this procedure was not successful and the patient suffered several flares. Because of that golimumab was suspended after 12 months of treatment and changed to TCZ. At the onset of TCZ therapy the patient had cystoid macular oedema (CME) in her left eye that had disappeared a week after the first TCZ infusion. This procedure yielded a dramatic improvement in CME (Fig. 1).

In the other patient with uveitis secondary to Behçet's disease (case 3 from Table I), combined treatment with ADA and MTX was started because of uveitis refractory to immunosuppressive therapy. Despite this procedure, the patient experienced new episodes of reactivation of intraocular inflammation therefore ADA was discontinued after 6 months of therapy. At that time, it was decided to initiate IFX combined with MTX. The drug was started at a loading dose of 5 mg/kg at 0, 2, 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks. At 6 months IFX therapy was stopped for persistent reactivations of uveitis and TCZ treatment was started. Despite the residual damage that this patient already had as the result of recurrent episodes of intraocular inflammation, 3 months after the onset of TCZ inactivity of the vitritis, retinal vasculitis and CME was achieved in both eyes.

Overall, the following ocular complications were observed in this series at the time of TCZ onset: macular oedema (3

Table I. Main demographic, clinical features and treatment of 3 patients treated with tocilizumab because of refractory uveitis.

Patient number	Gender/age (years)	Associated rheumatic disease	Synthetic immunosuppressant before first biologic drug	Biologic drugs before TCZ	Associated synthetic immunosuppressant with TCZ	Follow-up with TCZ (months)	Active uveitis at the last visit on TCZ therapy	BCVA at TCZ onset; BCVA at last visit on TCZ (OD/OS)
1	Woman / 37	Rheumatoid arthritis	MTX, CsA	IFX, ADA	MTX	9	no	0.8; 1
2	Woman / 42	Behçet´s disease	MTX, CsA, AZA	ADA, GLM	None (monotherapy)	1	yes	0.6/0.4; 0.8/0.5
3	Woman / 67	Behçet´s disease	MTX, CsA	ADA, IFX	None (monotherapy)	12	no	0.01/0.01; 0.01/0.01

MTX: methotrexate; CsA: cyclosporine; AZA: azathioprine; IFX: infliximab; ADA: adalimumab; GLM: golimumab; TCZ: tocilizumab; BCVA: best corrected visual acuity; OD: right eye; OS: left eye.

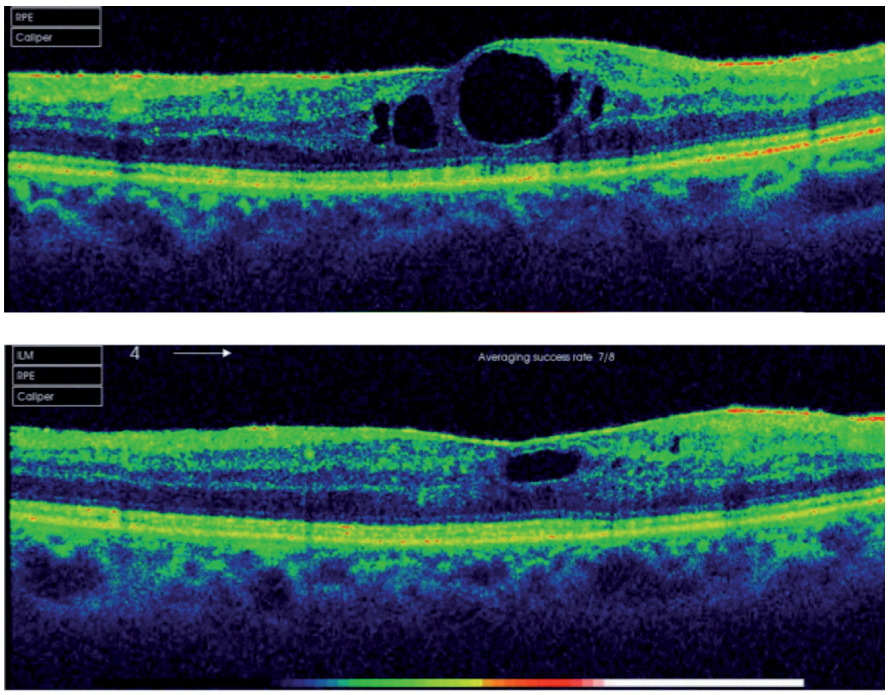


Fig. 1. OCT image of a patient with Behçet's disease before and 1 month after initiating tocilizumab therapy.

eyes), retinal vasculitis (4 eyes) and impairment of visual acuity (VA) (3 eyes). By the use of TCZ the best corrected visual acuity (BCVA) remained stable in 3 eyes, and improved in the other 3 eyes. After a mean follow-up of 7.3±5.7 (range 1–12) months all patients undergoing TCZ therapy experienced improvement and inactivity intraocular inflammation was achieved in 3 eyes. In addition, none of the patients had side effects during treatment with this drug. Figure 2 summarises the improvement of uveitis following the onset of TCZ therapy observed in these patients.

Discussion

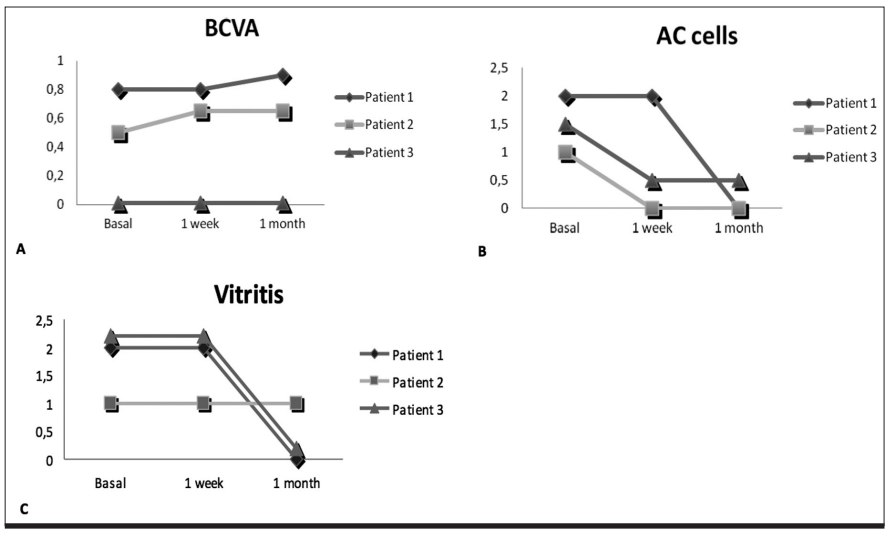
We report on 3 cases of uveitis refractory to synthetic conventional immunosuppressive drugs and at least one anti-TNF-α drug that responded favourably to TCZ.

There are many studies demonstrating the efficacy of anti-TNF-α drugs, in particular ADA and IFX, in the treatment of non-infectious refractory uveitis (2, 4, 5). However, information showing the efficacy of TCZ in the treatment of uvetis refractory to other biologic agents is scarce. It is probably due to the fact that TCZ is a relatively new drug and also because TCZ is an off-label indication for uveitis (13-17). Tocilizumab is a new humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), which has been

Table II. Literature review of patients with refractory uveitis treated with tocilizumab including our present series*.

	Hirano *et al*. (13)	Museliere *et al*. (14)	Tappeiner *et al*. (15)	Oshitari *et al*. (16)	Adan *et al*. (17)	Calvo-Río *et al*. present series*
Number of cases	1	2	3	1	5	3
Underlying disease	Behçet's disease	Birdshot, idiopathic	JIA	Multicentre Castleman disease	Birdshot (n=3), JIA (n=1), idiopathic (n=1)	RA (n=1), Behçet's disease (n=2)
Age (mean±SD), years	35	48±29.7	18.3±0.6	58	49.4	48.6±16.1
Uveitis pattern	?	Posterior uveitis bilateral, Panuveitis OD	2 anterior bilateral uveitis, 1 anterior uveitis OS	panuveitis	with uveítis-related CME	3 panuveitis
Previous treatment	Colchicine, CsA, IFX	MTX, AZA, MMF, ADA,	MTX, AZA, ETN, ADA, ABA	steroids	CyA, MTX,IFX, ADA, RTX, ABA, MMF	MTX, CsA, IFX, ADA, GLM
Reason for using TCZ	oral ulcers, erythema nodosum, and uveitis	CME, Uveitis relapse	Refractory uveitis	Uncontrolled intraocular pressures	Refractory uveitis-CME	Uveitis relapse
TCZ regimen	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 2-3 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks
Ocular inflammation following TCZ	Inactivity	Improvement	2 Inactive, 1 Active	Inactivity	Inactivity	2 Inactivity, 1 Improvement
Adverse effects by TCZ	Transient increase of LDL-cholesterol	None	None	None	None	None
Months in treatment with TCZ (mean± SD)	12	7±1.4	8.6±3	12	8.4	7.3±5.7
TCZ withdrawal	No	No	No	No	No	No

JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; OD: right eye; OS: left eye; MTX: methotrexate; CsA: cyclosporine A; AZA: azathioprine; MMF: Mycophenolate mofetil. ETN: etanercept; ADA: adalimumab; IFX: infliximab; GLM: golimumab; ABA: abatacept; TCZ: tocilizumab; CME: cystoid macular oedema; LDL: low density lipoproteins.



approved for the treatment of rheumatoid arthritis, systemic and poly-articular juvenile idiopathic arthritis, and Castleman's disease (8).

Dysregulation of IL-6 production causes imbalance in the Th17/Treg ratio. It was demonstrated that the blockade of IL-6 signaling in a murine model of autoimmune uveoretinitis suppressed the severity of uveoretinitis through Th17 and/or Th1 inhibition or Treg induction (10, 13, 18, 19).

Our results indicate that this biologic agent may also be effective in non-infectious uveitis refractory to anti-TNF-α drugs. Moreover, besides its efficacy to maintain intraocular inflammation inactivity, TCZ was useful to prevent further relapses in patients with recurrent episodes of uveitis.

Our observations on 3 patients were in keeping with former reports that showed good response to TCZ in 11 of 12 patients with immune-mediated uveitis refractory to other biologic agents in whom TCZ was prescribed (13-17). These studies along with our series are summarised in Table II. TCZ therapy led to improvement of ocular manifestations in all of them but in one patient the uveitis remained active. In our series inactivity of intraocular inflammation was achieved in 2 of the 3 patients and in the other patient, although inactivity was not reached, improvement in all ocular parameters was achieved.

TCZ dose approved for the use in rheumatoid arthritis in the USA is 4 mg/kg/every 4 weeks. In contrast, in Europe the dose is 8 mg/kg/every 4 weeks. We feel the initial dose of TCZ required in cases of refractory uveitis should be 8 mg/kg/every 4 weeks. We support our statement on the fact that refractory uveitis can lead to blindness. Therefore, in these cases the initial therapy must be aggressive to control ocular inflammation and prevent visual impairment.

Another issue so far unanswered is whether in refractory uveitis TCZ should be used alone or in combination with MTX. A comparative study on patients with refractory uveitis undergoing TCZ therapy alone or in combination with MTX is required to shed light on this question.

In conclusion, TCZ appears to be an effective and safe therapy for the management of patients with uveitis refractory to anti-TNF-α drugs. Although our results are certainly promising, further studies encompassing larger series of patients are needed to consider TCZ as the first biologic drugs to be used in patients with non-infectious uveitis refractory to synthetic conventional immunosuppressive drugs.

References

1. CHANG JH, WAKEFIELD D: Uveitis: a global perspective. *Ocul Immunol Inflamm* 2002; 10: 263-79.
2. 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.
3. SMIT RL, BAARSMA GS: Epidemiology of uveitis. *Curr Opin Ophthalmol* 1995; 6: 57-61.
4. ARIDA A, FRAGIADAKI K, GIAVRI E, SFIKAKIS PP: Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. *Semin Arthritis Rheum* 2011; 41: 61-70.
5. 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: 895-900.
6. SHARMA SM, NESTEL AR, LEE RWJ *et al*.: Clinical review: anti-TNF alpha therapies in uveitis: perspective on 5 years of clinical experience. *Ocul Immunol Inflamm* 2009: 17: 403-14.
7. PEREZ VL, PAPALIODIS GN, CHU D, ANZAAR F, CHRISTEN W, FOSTER CS: Elevated levels of interleukin 6 in the vitreous fluid of patients with pars planitis and posterior uveitis: the Massachusetts eye & ear experience and review of previous studies. *Ocul Immunol Inflamm* 2004; 12: 193-201.
8. TANAKA T, OGATA A, NARAZAKI M: Tocilizumab for the treatment of rheumatoid arthritis. *Expert Rev Clin Immunol* 2010; 6: 843-54.
9. TANAKA T, NARAZAKI M, KISHIMOTO T: Anti-interleukin-6 receptor antibody, tocilizumab, for the treatment of autoimmune diseases. *FEBS Lett* 2011; 585: 3699-709.
10. YOSHIMURA T, SONODA K-H, OHGURO N *et al*.: Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis. *Rheumatology* 2009; 48: 347-54.
11. ISHIHARA K, HIRANO T: IL-6 in autoimmune disease and chronic inflammatory proliferative disease. *Cytokine Growth Factor Rev* 2002; 13: 357-68.
12. DESCHENES J, MURRAY PI, RAO NA, NUSSENBLATT RB: International Uveitis Study Group (IUSG) clinical classification of uveitis. *Ocul Immunol Inflamm* 2008; 16: 1-2.
13. HIRANO T, OHGURO N, HOHKI S *et al*.: A case of Behçet's disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Mod Rheumatol* 2012; 22: 298-302.
14. MUSELIER A, BIELEFELD P, BIDOT S, VINIT J, BESANCENOT JF, BRON A: Efficacy of tocilizumab in two patients with anti-TNF-alpha refractory uveitis. *Ocul Immunol Inflamm* 2011; 19: 382-3.
15. TAPPEINER C, HEINZ C, GANSER G, HEILIGENHAUS A: Is tocilizumab an effective option for treatment of refractory uveitis associated with juvenile idiopathic arthritis? *J Rheumatol* 2012; 39: 1294-5.
16. OSHITARI T, KAJITA F, TOBE A *et al*.: Refractory uveitis in patient with castleman disease successfully treated with tocilizumab. *Case Rep Ophthalmol Med* 2012; 2012: 968180.
17. ADÁN A, MESQUIDA M, LLORENÇ V *et al*.: Tocilizumab treatment for refractory uveitis-related cystoid macular edema. *Graefes Arch Clin Exp Ophthalmol* 2013; 251: 2627-32.
18. HOHKI S, OHGURO N, HARUTA H *et al*.:Blockade of interleukin-6 signaling suppresses experimental autoimmune uveoretinitis by the inhibition of inflammatory Th17 responses. *Exp Eye Res* 2010; 91: 162-70.
19. HARUTA H, OHGURO N, FUJIMOTO M *et al*.: Blockade of interleukin-6 signaling suppresses not only Th17 but also interphotoreceptor retinoid binding protein-specific Th1 by promoting regulatory T cells in experimental autoimmune uveoretinitis. *Invest Opthalmol Vis Sci* 2011; 52: 3264-71.