Anti-IL6-Receptor Tocilizumab in Refractory and Noninfectious Uveitic Cystoid Macular Edema: Multicenter Study of 25 Patients

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• PURPOSE: Cystoid macular edema (CME) is a leading cause of blindness. This study assessed the efficacy and safety of tocilizumab (TCZ) in refractory CME.

• DESIGN: Retrospective case series.

• METHODS: Patients with CME secondary to noninfectious uveitis who had inadequate response to corticosteroids and at least 1 conventional immunosuppressive drug, and in most cases to other biological agents, were studied. CME was defined as central retinal thickness greater than 300 μm. The primary outcome measure was macular thickness. Intraocular inflammation, best-corrected visual acuity (BCVA), and corticosteroid-sparing effect were also analyzed.

• RESULTS: A total of 25 patients (mean ± standard deviation age 33.6 ± 18.9 years; 17 women) with CME were assessed. Underlying diseases associated with uveitis-related CME are juvenile idiopathic arthritis (n = 9), Behçet disease (n = 7), birdshot retinochoroidopathy (n = 4), idiopathic (n = 4), and sarcoidosis (n = 1). The ocular patterns were panuveitis (n = 9), anterior uveitis (n = 7), posterior uveitis (n = 5), and intermediate uveitis (n = 4). Most patients had CME in both eyes (n = 24). TCZ was used in monotherapy (n = 11) or combined with conventional immunosuppressive drugs. Regardless of the underlying disease, compared to baseline, a statistically significant improvement in macular thickness (415.7 ± 177.2 vs 259.1 ± 499.5 μm; $P = .00009$) and BCVA (0.39 ± 0.31 vs 0.54 ± 0.33; $P = .0002$) was obtained, allowing us to reduce the daily dose of prednisone (15.9 ± 13.6 mg/day vs 3.1 ± 2.3 mg/day; $P = .002$) after 12 months of therapy. Remission was achieved in 14 patients. Only minor side effects were observed after a mean follow-up of 12.7 ± 8.34 months.

• CONCLUSION: Macular thickness is reduced following administration of TCZ in refractory uveitis-related CME. (Am J Ophthalmol 2019;200:85–94. © 2019 Elsevier Inc. All rights reserved.)

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CYSTOID MACULAR EDEMA (CME) IS A SWELLING OF the macula with fluid accumulation within the intracellular spaces of the retina, leading to the formation of cystic spaces.[1] CME represents the leading cause of blindness in patients with uveitis.[2–5]

Underlying diseases associated with uveitis-related CME are sarcoidosis, juvenile idiopathic arthritis (JIA), birdshot retinochoroidopathy, and Behçet disease.[2,4] Most uveitis may involve complications of CME and blindness, depending on the underlying disease, anatomic pattern, and chronicity of inflammation. CME-related blindness has been reported in 5%–72% of patients with sarcoid-associated uveitis,[6–8] 16%–22% of patients with JIA-associated uveitis,[9–11] and 25%–42% of patients with Behçet disease.[12,13] According to anatomic location, panuveitis (36%–66%) and intermediate

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uveitis (40%–60%) are the patterns most commonly associated with the above-mentioned diseases.[2,14]

CME is the consequence of the exposure of the inner blood-retinal barrier to intraocular inflammatory mediators, including interleukin-6 (IL-6).[2,9,15] Increased IL-6 expression has been found in intermediate and posterior uveitis[9] and may be correlated with macular edema, directly, by increasing endothelial permeability, or indirectly, by inducing vascular endothelial growth factor (VEGF).[16,17]

CME should be treated quickly and intensely with regional corticosteroid injections and systemic corticosteroids, conventional immunosuppressive drugs, or biologic agents,[15] such as monoclonal anti–tumor necrosis factor (anti-TNF-α) antibodies. Some patients may show partial or no response to these treatments after a minimum treatment period of 1 month.

Tocilizumab (TCZ, Actemra; Genentech, South San Francisco, California, USA), a humanized antibody, binds to soluble and membrane-bound IL-6 receptors and inhibits downstream signaling to inflammatory mediators. Several studies have reported the efficacy of TCZ in CME.[18] In most cases, data are based on small case series[15,19–24]; however, in the STOP-Uveitis Study,[25] Sepah and associates reported the primary endpoint analyses of the safety and efficacy of 2 different doses of intravenous infusions of TCZ (4 and 8 mg/kg, respectively, every 4 weeks) until month 6 in 37 patients with noninfectious intermediate, posterior, or panuveitis.

After a review of previous studies on TCZ treatment in patients with CME was performed, the present study was conducted to assess the efficacy of TCZ (administered intravenously or subcutaneously) in 25 patients with noninfectious uveitis-associated CME, refractory to corticosteroids and at least 1 conventional immunosuppressive drug, and in most cases (n = 22) to other biologic agents.

PATIENTS AND METHODS

• **DESIGN AND ENROLLMENT CRITERIA:** This study is a retrospective case series study conducted in 11 referral centers in Spain that evaluated the effect of TCZ administered intravenously or subcutaneously to 25 subjects with refractory noninfectious uveitis, followed up over a 12-month period. TCZ is an off-label indication for uveitis, with or without CME. Therefore, written, informed consent was requested and obtained from all patients, and the drug administration protocol was approved by the drugs and therapeutics committee of each selected hospital.

Institutional review board/ethical approval was also obtained from Spanish national authorities (NVR-2018.124). TCZ was administered intravenously (iv) at a dose of 4 mg/kg or 8 mg/kg every 4 weeks, or subcutaneously (sc) at a dose of 162 mg/week. The primary endpoint of the study was at month 12, but response was assessed by comparing to baseline at weeks 1 and 2, and at months 1, 2, 3, 6, and 12. Prior to TCZ administration, 22 of 25 patients had received treatment with corticosteroids (local or systemic), at least 1 conventional synthetic immunosuppressive drug, and a biologic agent (generally an anti-TNF-α inhibitor), and had presented partial or no response to these therapies. Only 3 patients received TCZ as the first biologic agent.

Macular edema was considered persistent or unresponsive to corticosteroids, to synthetic immunosuppressive drugs, or to biologic agents when central foveal thickness was ≥300 μm and/or presence of cystic spaces was confirmed after regular evaluations while patients were receiving the above-mentioned treatments.

• **WORKING DEFINITIONS AND THERAPEUTIC SCHEME:** Macular thickening was defined as central macular thickness of >300 μm on optical coherence tomography (OCT), and CME included the presence of radially oriented cystoid spaces in the macula, visualized by OCT.

Malignancy or systemic infectious diseases, including hepatitis B or hepatitis C infection, were excluded prior to TCZ administration, as previously described.[6,9,22,26–30] As indicated in the Spanish National Guidelines, all patients were tested for latent tuberculosis by tuberculin purified protein derivative skin test and/or an interferon-γ assay (QuantiFeron) and a chest radiograph. If positive results were obtained, prophylactic treatment with isoniazid was initiated at least 4 weeks prior to initiation of TCZ treatment, and was maintained for 9 months.

Uveitis was anatomically classified according to the Standardization of Uveitis Nomenclature (SUN) Working Group criteria.[31] Remission was defined as no disease activity for at least 3 months.[31] A relapse was defined as the appearance of a new flare of uveitis after ≥3 months of inactivity without treatment.[31]

A standard 1-hour intravenous infusion of 8 mg/kg TCZ was given to 23 of 25 patients at 4-week intervals. One patient with JIA received an intravenous infusion of 8 mg/kg every 2 weeks, and the patient with sarcoidosis was treated with 162 mg (sc)/week.

Partial information on some of the patients included in this series of 25 patients was reported in previous studies.[9,15,20,24]

• **OUTCOME MEASURES:** We retrospectively assessed anatomic (central macular thickness) and functional (BCVA, intraocular inflammation, and prednisone dose–sparing) improvements in refractory uveitic CME following TCZ use in multiple uveitis entities. These variables were analyzed at baseline, at weeks 1 and 2, and at months 1, 3, 6, and 12.

Macular thickness was measured by high-definition optical coherence tomography (HD-OCT). All HD-OCT scans were performed using Cirrus high-definition OCT

TABLE 1. Baseline Main General Features of the 25 Patients With Refractory and Severe Uveitic Cystoid Macular Edema

Feature	Value
Age, mean ± SD, years	33.6 ± 18.9
Sex, female/male, n	17/8
No. of affected eyes, n	49
Systemic inflammatory diseases, n	
JIA	9
Behçet	7
Birdshot	4
Idiopathic	4
Sarcoidosis	1
Pattern of uveitis, n	
Bilateral/unilateral	24/1
Anterior	7
Intermediate	4
Posterior	5
Panuveitis	9
Previous conventional immunosuppressive agents, n	
MTX	19
CsA	17
AZA	2
CYC	1
SZP	1
MMF	3
LFN	2
Thalidomide	1
Number of biological agents before TCZ, n	
1	13
2	6
3	1
4	1
5	1

AZA = azathioprine; CME = cystoid macular edema; CsA = cyclosporine A; CYC = cyclophosphamide; JIA = juvenile idiopathic arthritis; LFN = leflunomide; MMF = mycophenolate mofetil; MTX = methotrexate; SZP = sulfasalazine; TCZ = tocilizumab.

(Carl Zeiss, Oberkochen, Germany). Scans were obtained using a 512 × 128 scan pattern.

Intraocular inflammation was assessed according to the SUN Working Group grading schemes.[31] Inactive anterior uveitis was defined as <1 cell per field on standard slit-lamp examination (grade 0). Following SUN recommendations, improvement of anterior uveitis activity was defined as either a 2-step decrease in the level of inflammation or decrease to grade 0 (grading scale: 4, 3, 2, 1, 0.5, and 0).[31]

Vitritis was assessed using the Nussenblatt scale.[32] Vitreous activity can range from the greatest amount of activity (4+: the optic nerve head is obscured) to the lesser intermediate points (3+: the borders of the optic nerve are quite blurry; 2+: permits better visualization of retinal vessels; 1+: permits a better definition of the optic nerve head and retinal vessels) to no evident vitreal haze at all (trace 0).[32]

Visual acuity was assessed according to BCVA and determined using the Snellen chart. According to this test, 20/20 vision (or 20/20 visual acuity) is considered normal vision (the subject can read a letter that most individuals can read at a distance of 20 feet). For the purpose of the present study, 20/20 vision (normal vision) is expressed as 1.0, and 0/20 vision is expressed as 0.0.[32]

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using Statistica software (StatSoft, Tulsa, Oklahoma). Results were expressed as the mean ± standard deviation or median (interquartile range [IQR]), as appropriate. Wilcoxon signed rank test was used to compare continuous variables prior to and after TCZ therapy. Results were reported considering the number of affected eyes.

RESULTS

• **BASELINE DATA:** Twenty-five patients (17 women/8 men) with uveitis-associated CME refractory to conventional immunosuppressive therapy, and in most cases (n = 22) to other biologic agents, were enrolled in the study (Table 1). Mean age was 33.6 ± 18.9 years. Underlying diseases were JIA (n = 9), Behçet disease (n = 7), birdshot retinochoroidopathy (n = 4), idiopathic (n = 4), and sarcoidosis (n = 1). Patterns of uveitis were panuveitis (n = 9), anterior uveitis (n = 7), posterior uveitis (n = 5), and intermediate uveitis (n = 4). Most patients had bilateral involvement (n = 24). Median time from uveitis diagnosis to TCZ administration was 112 months (IQR 11–364 months).

• **PREVIOUS TREATMENT BEFORE TOCILIZUMAB:** Prior to TCZ infusion, intraocular corticosteroids (n = 22) and intravenous methylprednisolone (n = 7) were used. The conventional immunosuppressive drugs given prior to TCZ administration were as follows: methotrexate (MTX) 15–20 mg/m^2/week (n = 19); cyclosporine A (CsA) 2–5 mg/kg/day (n = 17); azathioprine 1–4 mg/kg/day (n = 2); leflunomide pediatric dose of 10 mg/day for children weighing 20–40 kg and 20 mg/day for children weighing >40 kg, and adult dose of 100 mg/daily for 3 days and then 10–20 mg/day (n = 2); sulfasalazine 2–3 g/day (n = 1); thalidomide 100–200 mg/day (n = 1); mycophenolate 2–3 g/day (n = 3); acetazolamide 1 g/day (n = 1); cyclophosphamide 1–2 mg/kg/day administered orally (n = 1).

Most patients had also received other biologic agents (Figure 1): adalimumab (ADA) 40 mg (sc) every 1 or 2 weeks (n = 19); etanercept (ETN) 12.5–50 mg (sc)/week (n = 2); infliximab (IFX) 3–5 mg/kg (iv) at weeks 0, 2, and 6, followed by a maintenance dose every 4, 6, or 8 weeks (n = 8); abatacept (ABA) 10 mg/kg (iv) at weeks 0, 2, and 6, followed by a maintenance dose every 4 weeks (n = 3); rituximab (RTX) in a single course of 2 doses of 1 g (iv) 2 weeks apart (n = 2); golimumab (GLM) 50 mg (sc)/month (n = 2); daclizumab

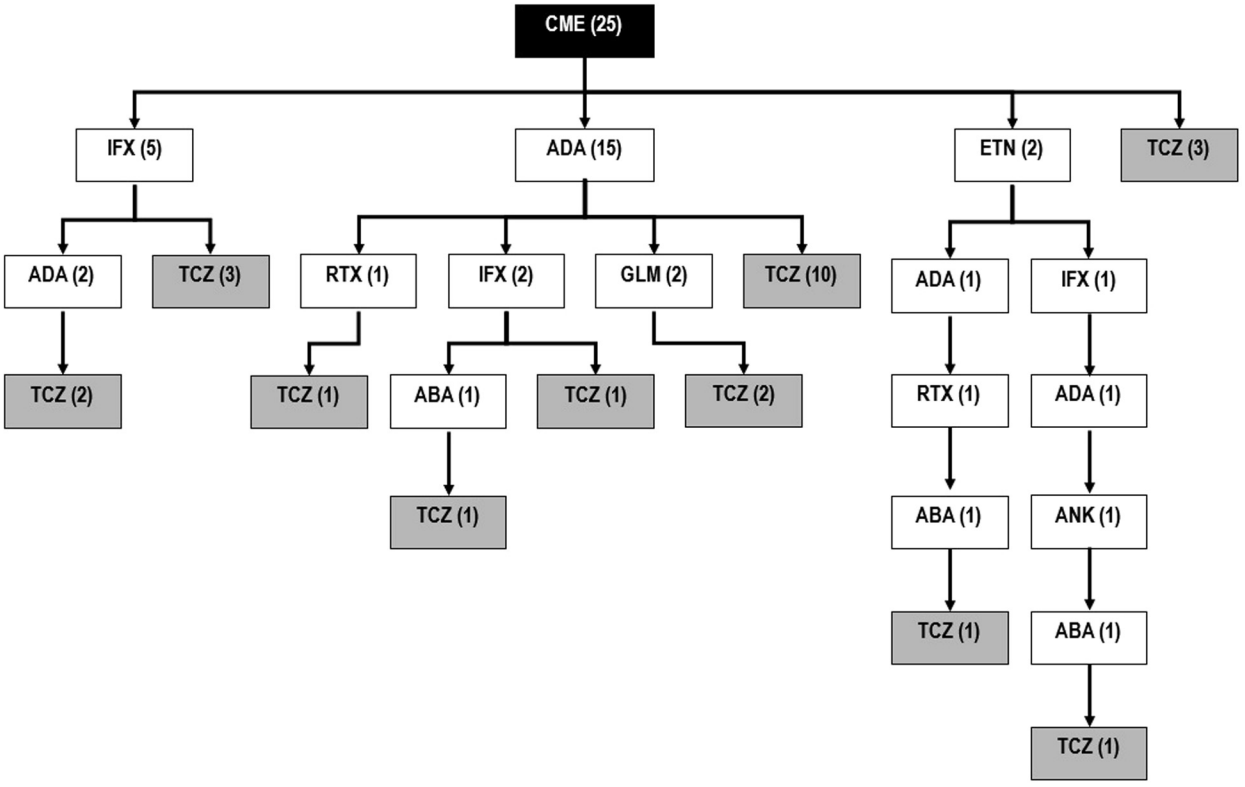

FIGURE 1. Flow chart showing the biologic therapy used in 25 patients with refractory cystoid macular edema–associated uveitis that required tocilizumab (TCZ). Number of cases are shown in parentheses. ADA = adalimumab; ANK= anakinra; ETN = etanercept; GLM = golimumab; IFX = infliximab.

1–2 mg/kg every 2 or 4 weeks (n = 1); and anakinra 100 mg (sc)/day (n = 1).

• **OUTCOME VARIABLES AFTER TOCILIZUMAB TREATMENT:** TCZ was used in combination with conventional immunosuppressive drugs in 12 of 25 patients (MTX in 6 patients, CsA in 5 patients, and leflunomide in 1 patient).

Compared to baseline, a statistically significant reduction in macular thickness (432.7 ± 161.8 μm vs 259.1 ± 49.5 μm; $P < .0001$) was observed up until and including month 12 of treatment (Figure 2, Top). This improvement was independent of age, sex, and underlying disease (Figure 2, Bottom). Moreover, most intraocular inflammation parameters showed a rapid improvement after initiation of TCZ therapy. According to the SUN classification system, a 2-step decrease in the level of inflammation or a decrease to grade 0 in the level of inflammation was reported in most patients. Twenty-one of 23 eyes (91%) affected at baseline showed reduction in the number of anterior chamber cells at month 12. In addition, resolution of prominent vitritis was observed in 19 of 27 eyes (70.3%) affected at baseline. Mean BCVA improved from 0.39 ± 0.31 at baseline to 0.54 ± 0.33 ($P < .0001$) at month 12 (Figure 3). Mean prednisone dose was reduced from 15.9 ± 13.6 mg/day at baseline to 3.1 ± 2.3 mg/day at month 12 ($P = .002$). Ocular remission was achieved in 14 patients. Interestingly, after a mean follow-up of 12.7 ± 8.34 months, the only relevant side effects observed were nausea (n = 1), and viral conjunctivitis and bullous impetigo (n = 1).

DISCUSSION

WE STUDIED 25 PATIENTS WITH CME REFRACTORY TO CONventional immunosuppressive drugs and, in most cases (n = 22), also to other biologic agents. After TCZ infusion, most patients experienced a rapid and maintained response.

Uveitis is the fifth-leading cause of visual impairment[33] and the third-leading cause of blindness in developed countries (2.8%–10%).[34] CME is a painless disorder first described in 1947.[35] It is the most common cause of decreased vision and a common sequela of retina injuries, such as intraocular inflammation, central or branch retinal vein occlusion, and diabetic retinopathy. In addition, it is a common postoperative complication of cataract surgery.[5] It is well known that CME should be treated aggressively to improve the visual prognosis. Only corticosteroids and

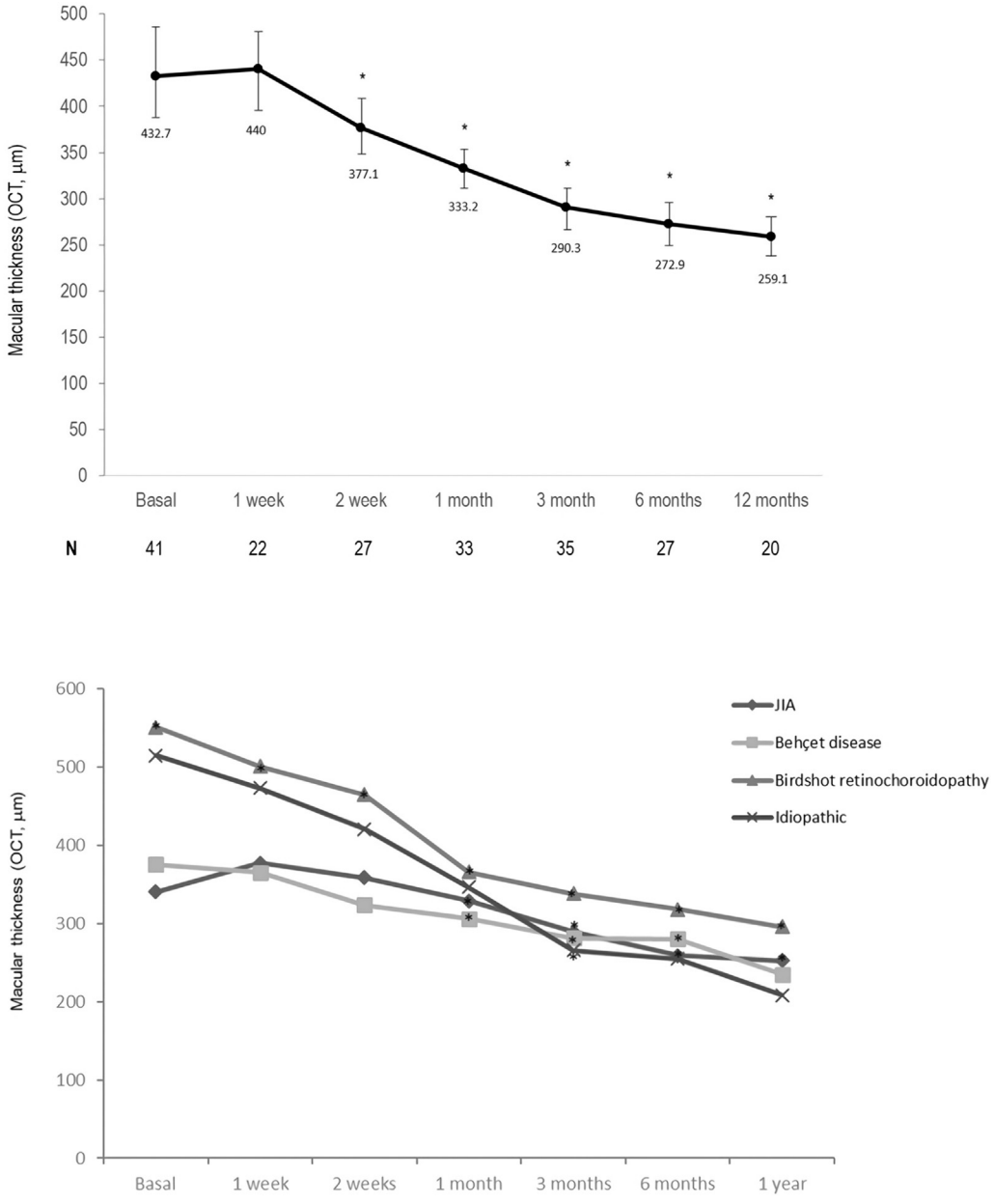

FIGURE 2. (Top) Time course of macular thickness during the study (affected eyes). Bars represent mean and standard error. *P < .001. (Bottom) Macular thickness: Improvement following tocilizumab therapy for each underlying disease. *P < .05. JIA = juvenile idiopathic arthritis; OCT = optical coherence tomography.

adalimumab are currently registered for use in uveitis, even though systemic immunomodulatory drugs are widely used in clinical practice.

TCZ is a humanized monoclonal antibody against soluble and membrane-bound IL-6 receptor that has been approved for the treatment of autoimmune and inflammatory diseases, such as rheumatoid arthritis, systemic and polyarticular juvenile arthritis, and Castleman's disease.[36] TCZ has shown efficacy in the treatment of different systemic diseases, including vasculitis syndromes.[37–40] Interestingly, in the experimental model of autoimmune uveitis in mice, treatment with an anti-IL-6 receptor antibody resulted in a dramatic reduction of uveal inflammation.[41] The mechanisms by which TCZ leads to clinical improvement in patients with uveitis are not fully understood; even CME pathogenesis is not totally clear nowadays. However, TCZ has demonstrated efficacy in patients with refractory ocular inflammatory diseases, including those with CME.[9,11,19–23,26,42–47]

The most frequent causes of noninfectious CME secondary to inflammatory diseases are HLA-B27-positive anterior uveitis, JIA, intermediate uveitis (owing to sarcoidosis, multiple sclerosis, and pars planitis), posterior uveitis (in systemic

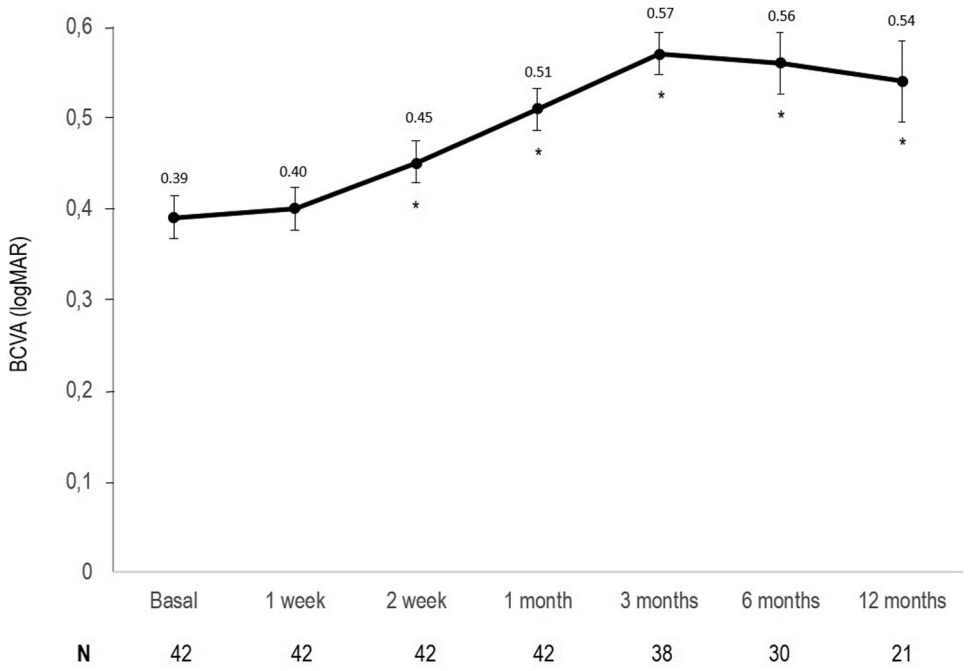

FIGURE 3. Mean changes of best-corrected visual acuity (BCVA) after tocilizumab therapy (affected eyes). Bars represent mean and standard error. *$P < .001$.

diseases, such as sarcoidosis and Behçet disease), and birdshot retinochoroidopathy.[33] The visual prognosis of uveitis-related CME depends on the status of the outer retinal layers and on uveitis duration, type, and underlying disease.[33] Chronic CME associated with posterior uveitis usually requires a step-by-step therapeutic approach, and owing to its refractoriness, immunosuppressive therapy is also necessary in most cases. In these situations, patients may require therapeutic assessment in a tertiary care center.[33]

Several hypotheses have been proposed to explain why diverse and unrelated conditions may lead to macular edema. Initial circumstances that may change anatomic conditions are metabolic changes (hyperlipidemia, albuminuria), ischemic complications (cardiovascular disease), hydrostatic forces, and various toxic effects (smoking, topical applications of prostaglandin analogues, zidovudine, and rifabutin) on the retinal cells, vessels, and retinal pigment epithelium (RPE).[2] These circumstances may favor fluid leaks across the retinal vessel wall from retinal vessels and through the RPE, thus leading to the accumulation of fluid in the macular area, usually in the outer plexiform layer.[2] Then, it is possible that inflammatory mediators play an essential initiating role in the development of inflammatory CME, but the exact factors and events responsible for CME chronicity have not yet been identified.[2]

Several studies have attempted to explain the inflammation cascade that occurs in CME and have drawn attention to IL-6 importance. Under physiological conditions, IL-6 is barely detectable in serum. However, a significant elevation of IL-6 in ocular fluids has been reported in animal models[36,41,47] and in patients during early phases of inflammation.[41,47] This IL-6 increase is recognized as an essential factor in inducing the early phase of Th17 differentiation from naïve T cells in combination with TGF-β.[36] Th17 cells further produce IL-17, IL-6, and TNF-α, stimulating the whole inflammation cascade, which results in tissue damage and chronic inflammation.[36] In these situations, IL-6 blockade may suppress autoantibody production or correct the imbalance of Th17.[47]

Moreover, IL-6 contributes to the pathogenesis of macular edema directly, by increasing endothelial permeability, or indirectly, by inducing VEGF through its receptor-alpha.[17] The crosstalk between IL-6 and VEGF induces an elevation of VEGF production in the vitreous fluid,[17] which may play a key role in increasing blood-retinal barrier permeability and disruption.[16] The upregulation of VEGF may contribute to retinal detachment.[17] All things considered, vitreous fluid levels of VEGF and IL-6 are significantly correlated with the severity of macular edema.[16]

The positive effect of TCZ on uveitis-related CME has been reported in several case series and in a clinical trial. An updated literature review on this topic is summarized in Table 2. The first case report was published by Muselier and associates in 2011.[23] In 2014, the study by Papo and associates[44] included the largest series of patients with refractory CME treated with TCZ, and it showed improvement of visual acuity in 6 of 8 patients. The 2 patients who did not respond were those with the most severe ocular inflammation at the time of initiation of TCZ therapy, with significant loss of visual acuity in both eyes.

TABLE 2. Literature Review of Studies of Patients With Refractory Uveitis-related Cystoid Macular Edema Treated With Tocilizumab

	Muselier et al, 2011[23]	Adán et al, 2013[15]	Adán et al, 2013[42]	Adán et al, 2014[43]	Papo et al, 2014[44]	Mesquida et al, 2014[20]	Tappeiner et al, 2016[45]	Deroux et al, 2016[46]	Deuter et al, 2017[21]	Mesquida et al, 2017[24]	Sepah et al, 2017[25]	Vegas-Revenga et al, Present Series
No. of patients with CME	2	5	1	1	2	7	5	1	5	12	37	25
Sex (f/m), n	2/0	5/0	1/0	1/0	2/0	7/0	NS	1/0	3/2	10/2	22/15	17/8
Age, years	27–69	30–68	56	29	21–47	23–70	7–30	23	23–57	15–62	26–60	12–75
Underlying disease	BSRC and idiopathic uveitis	BSRC (n=3), JIA (n=1), idiopathic panuveitis (n=1)	Idiopathic panuveitis	JIA	Spondyloarthropathy (n=1), idiopathic panuveitis (n=1)	BSRC (n=3), JIA (n=3), idiopathic uveitis (n=1).	JIA	BSRC	JIA (n=2), ankylosing spondylitis (n=1), rheumatoid arthritis (n=2)	JIA (n=6), BSRC (n=2), idiopathic panuveitis (n=2), sympathetic ophthalmia (n=1), ankylosing spondylitis (n=1)	BSRC (n=2), sarcoidosis (n=2), Behçet disease (n=1), Vogt-Koyangi-Harada syndrome (n=2), punctate inner choroiditis (n=1), TINU syndrome (n=1) idiopathic uveitis (n=4)	JIA (n=9), BSRC (n=4), sarcoidosis (n=1), Behçet disease (n=7), idiopathic uveitis (n=4)
Uveitis pattern	Posterior uveitis + CME, vitritis + vasculitis + CME	Uveitis-related CME	Severe bilateral CME	JIA-associated uveitis complicated with CME and VPRT	Panuveitis + CME	Posterior uveitis + CME (n=6) and panuveitis + CME (n=1)	JIA-associated anterior uveitis complicated with CME	Posterior uveitis + CME	Chronic anterior uveitis + CME (n=3), acute anterior uveitis + CME (n=1), intermediate uveitis + CME (n=1).	ME with quiescent uveitis	Intermediate uveitis (n=6), posterior uveitis (n=5), panuveitis (n=26)	Anterior uveitis (n=7), intermediate uveitis (n= 4), posterior uveitis (n=5) and panuveitis (n= 9)
Previous treatment	MTX, AZA, MMF, ADA	MTX, CsA, MMF, IFX, ADA, RTX, ABA	MTX, CsA, IFX, ADA	MTX, IFX, ADA	MTX, AZA, CYC, CsA, IFN-α, IFX, ADA, ABA, ANK	MTX, CsA, MMF, IFX, ADA, ABA, RTX	MTX, CsA, LFN, IFX, ADA, ABA.	MTX, AZA, CsA, IFX, ADA, ANK	MTX, MMF, CsA, LFN, Acet, ADA, ETN, ABA, GLM	MTX, MMF, CsA, ADA, IFX, ETN, ANK, GLM	MTX, MMF, Tacrolimus, ADA	DMARDs, IFX, ADA, ETN, GLM, RTX, ABA, ANK, DCZ
TCZ regimen	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks 4 mg/kg every 4 weeks	8 mg/kg every 4 weeks 4 mg/kg every 4 weeks	8 mg/kg/ every 4 weeks (n=23), 8 mg/kg/ every 2 weeks (n= 1), 162 mg/sc/ every week (n=1)

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TABLE 2. Literature Review of Studies of Patients With Refractory Uveitis-related Cystoid Macular Edema Treated With Tocilizumab (*Continued*)

	Muselier et al, 2011[23]	Adán et al, 2013[15]	Adán et al, 2013[42]	Adán et al, 2014[43]	Papo et al, 2014[44]	Mesquida et al, 2014[20]	Tappeiner et al, 2016[45]	Deroux et al, 2016[46]	Deuter et al, 2017[21]	Mesquida et al, 2017[24]	Sepah et al, 2017[25]	Vegas-Revenga et al, Present Series
Adverse effects related to TCZ	None	None	None	None	Leukopenia (n=1), thrombocytopenia (n=1)	NS	None	None	NS	Grade 1 neutropenia (n=1) and community-acquired pneumonia (n=1)	Neutropenia (n=2)	Nausea (n=1), viral conjunctivitis and bullous impetigo (n=1)
Months of TCZ treatment	6–8	6–12	6	12	7–25	12–18	3–12	12	4–35	24	6	1.5–31
Ocular outcome	Improvement (n=2)	Improvement (n=5)	Inactive	Improvement	Improvement (n= 2)	Inactive (n=2)	Improvement (n=5)	Inactive	Improvement (n=5)	Inactive (n=12)	Improvement (n=37)	Inactive (n=14)

ABA = abatacept; Acet = acetazolamide; ADA = adalimumab; ANK = anakinra; AZA = azathioprine; BSRC = birdshot retinochoroidopathy; CME = cystoid macular edema; CsA = cyclosporine A; CYC = cyclophosphamide; DCZ = daclizumab; DMARDS = disease modifying antirheumatic drugs; ETN = etanercept; GLM = golimumab; IFN-α = interferon alpha; IFX = infliximab; JIA = juvenile idiopathic arthritis; LFN = leflunomide; MMF = mycophenolate mofetil; MTX = methotrexate; NS = not specified; RTX = rituximab; TCZ = tocilizumab; TINU = tubulointerstitial nephritis and uveitis; VPRT = retinal vasoproliferative tumor.

In the last 2 years, 2 remarkable studies have been published, by Mesquida and associates[24] and by Sepah and associates.[25] Mesquida and associates[24] reported 12 patients with macular edema from a single center in Spain (Hospital Clinic of Barcelona). The baseline diseases of macular edema were juvenile idiopathic arthritis associated, birdshot retinochoroidopathy, idiopathic panuveitis, sympathetic ophthalmia, and ankylosing spondylitis. TCZ was administered in monotherapy at a dose of 8 mg/kg (iv) every 4 weeks, after a prior 3-month washout period for biologic agents. The dose of TCZ for CME most frequently used is 8 mg/kg (iv) every 4 weeks.[18–22,26,44] The improvement of CME after month 24 of TCZ therapy was highly significant.

The study by Sepah and associates[25] presents the largest series, with a total of 37 patients. Patients were selected from different centers in the United States and had the following underlying diseases: sarcoidosis, Vogt-Koyanagi-Harada syndrome, birdshot retinochoroidopathy, punctate inner choroiditis, Behçet disease, tubulointerstitial nephritis and uveitis (TINU) syndrome, and idiophatic uveitis. Twenty-two patients were treatment naïve, and 15 patients had been treated with local or systemic corticosteroids and/or immunomodulatory therapy. In the case of previously treated patients, immunomodulatory therapy was discontinued at least 30 days prior to baseline visit. The dose of systemic corticosteroids was tapered, beginning at the week 4 visit. Patients were randomized to receive TCZ at a dose of either 4 mg/kg or 8 mg/kg every 4 weeks until month 5.[25] As of month 6, patients were evaluated monthly, and if found to have active inflammation, they received additional TCZ infusions at the initially assigned dose until month 11, with a final study visit at month 12.[25] This study concluded that TCZ was effective in improving visual acuity and reducing vitreous haze and central macular thickness.

The present study is also a multicenter study that included 25 Spanish patients. Underlying inflammatory diseases were juvenile idiopathic arthritis, Behçet disease, birdshot retinochoroidopathy, sarcoidosis, and idiopathic panuveitis. Twenty-three of 25 patients had been refractory to a wide range of disease-modifying antirheumatic drugs (methotrexate, cyclosporine A, azathioprine, leflunomide, sulfasalazine, thalidomide, mofetil, acetazolamide, and cyclophosphamide) and biologic therapies (adalimumab, etanercept, infliximab, abatacept, rituximab, golimumab, daclizumab, and anakinra); in 1 patient, 5 different biologic agents were used until satisfactory response was achieved with TCZ.

Unlike our study, neither of the studies to which we are compared included a large number of patients who had been refractory to other therapies prior to TCZ treatment. In the study by Mesquida and associates, TCZ was used in monotherapy, with a prior washout period of 3 months. The study by Sepah and associates included treatment-naïve patients or patients who suspended treatment with other immunomodulatory drugs at least 30 days prior to TCZ, which in turn means that TCZ was used in the initial

stages of uveitis and in patients who had not previously suffered side effects from other drugs. In contrast, in our study, TCZ therapy was used in combination with immunomodulatory drugs in 12 of 25 patients. In addition, only 3 of 25 patients received TCZ as the first biologic therapy. In terms of drug doses and pathways of administration, it is noteworthy that in the study by Mesquida and associates TCZ was administered at a dose of 8 mg/kg (iv) every 4 weeks, and in the STOP-Uveitis study at doses of 4 mg/kg or 8 mg/kg (iv) every 4 weeks, while in our study TCZ infusions were given intravenously at a dose of 8 mg/kg every 2 or 4 weeks, or subcutaneously at a dose of 162 mg/week. Remission was achieved in 14 patients, and a significant decrease in CME, as well as improvement in visual acuity, was achieved in all 25 patients in a short time period, with minor side effects. Another remarkable finding was the rapid response after the first administration of TCZ, despite the prolonged course of CME in some cases.

In clinical trials, adverse events associated with TCZ include infections, infusion-related reactions, and gastrointestinal perforation.[47] Reactivation of tuberculosis has been rarely reported during TCZ treatment, compared with anti-TNF-α biologic therapy. However, screening and monitoring for tuberculosis, as well as for fungal infections, are mandatory during treatment.[47] Other laboratory abnormalities associated with the use of TCZ that should be considered are hyperlipidemia, elevated transaminase levels, and neutropenia.[47] However, in our study only minor side effects were reported.

There are some limitations in the study, including the small sample size and short follow-up period. However, our results are results from daily practice emphasizing the beneficial effect of TCZ in refractory CME.

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REFERENCES

1. Bringmann A, Reichenbach A, Wiedemann P. Pathomechanisms of cystoid macular edema. *Ophthalmic Res* 2004;36(5):241–249.
2. Rothova A. Inflammatory cystoid macular edema. *Curr Opin Ophthalmol* 2007;18(6):487–492.
3. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. *Br J Ophthalmol* 1996;80(9):844–848.
4. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. *Br J Ophthalmol* 1996;80(4):332–336.
5. de Smet MD, Okada AA. Cystoid macular edema in uveitis. *Dev Ophthalmol* 2010;47:136–147.
6. Riancho-Zarrabeitia L, Calvo-Río V, Blanco R, et al. Anti-TNF-α therapy in refractory uveitis associated with sarcoidosis: multicenter study of 17 patients. *Semin Arthritis Rheum* 2015;45(3):361–368.
7. Bonfioli AA, Orefice F. Sarcoidosis. *Semin Ophthalmol* 2005;20(3):177–182.
8. Varron L, Abad S, Kodjikian L, Sève P. [Sarcoid uveitis: Diagnostic and therapeutic update]. *Rev Med Interne* 2011;32(2):86–92.
9. Calvo-Río V, Santos-Gómez M, Calvo I, et al. Anti–interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis–associated uveitis refractory to anti–tumor necrosis factor therapy: a multicenter study of twenty-five patients. *Arthritis Rheumatol* 2017;69(3):668–675.
10. Angeles-Han ST, McCracken C, Yeh S, et al. Characteristics of a cohort of children with juvenile idiopathic arthritis and JIA-associated uveitis. *Pediatr Rheumatol Online J* 2015;13:19.
11. Zulian F, Martini G, Falcini F, et al. Early predictors of severe course of uveitis in oligoarticular juvenile idiopathic arthritis. *J Rheumatol* 2002;29(11):2446–2453.
12. 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(2):298–302.

13. Ghassemi F, Mirak SA, Chams H, et al. Characteristics of macular edema in Behcet disease after intravitreal bevacizumab injection. *J Ophthalmic Vis Res* 2017;12(1):44–52.
14. Grajewski RS, Boelke AC, Adler W, et al. Spectral-domain optical coherence tomography findings of the macula in 500 consecutive patients with uveitis. *Eye Lond* 2016;30(11):1415–1423.
15. Adán A, Mesquida M, Llorenç V, et al. Tocilizumab treatment for refractory uveitis-related cystoid macular edema. *Graefes Arch Clin Exp Ophthalmol* 2013;251(11):2627–2632.
16. Noma H, Funatsu H, Mimura T, Harino S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor in macular edema with central retinal vein occlusion. *Ophthalmology* 2009;116(1):87–93.
17. Zahir-Jouzdani F, Atyabi F, Mojtabavi N. Interleukin-6 participation in pathology of ocular diseases. *Pathophysiology* 2017;24(3):123–131.
18. Lopalco G, Fabiani C, Sota J, et al. IL-6 blockade in the management of non-infectious uveitis. *Clin Rheumatol* 2017;36(7):1459–1469.
19. Silpa-Archa S, Oray M, Preble JM, Foster CS. Outcome of tocilizumab treatment in refractory ocular inflammatory diseases. *Acta Ophthalmol (Copenh)* 2016;94(6):e400–e406.
20. Mesquida M, Molins B, Llorenç V, Sainz de la Maza M, Adán A. Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema. *Ophthalmology* 2014;121(12):2380–2386.
21. Deuter CME, Zierhut M, Igney-Oertel A, et al. Tocilizumab in uveitic macular edema refractory to previous immunomodulatory treatment. *Ocul Immunol Inflamm* 2017;25(2):215–220.
22. Calvo-Río V, Blanco R, Santos-Gómez M, et al. Efficacy of anti-IL6-receptor tocilizumab in refractory cystoid macular edema of birdshot retinochoroidopathy report of two cases and literature review. *Ocul Immunol Inflamm* 2016;1–6.
23. Muselier A, Bielefeld P, Bidot S, Vinit J, Besancenot J-F, Bron A. Efficacy of tocilizumab in two patients with anti-TNF-alpha refractory uveitis. *Ocul Immunol Inflamm* 2011;19(5):382–383.
24. Mesquida M, Molins B, Llorenç V, et al. Twenty-four month follow-up of tocilizumab therapy for refractory uveitis-related macular edema. *Retina* 2018;38(7):1361–1370.
25. Sepah YJ, Sadiq MA, Chu DS, et al. Primary (month-6) outcomes of the STOP-Uveitis Study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with non-infectious uveitis. *Am J Ophthalmol* 2017;183:71–80.
26. Calvo-Río V, de la Hera D, Beltrán-Catalán E, et al. Tocilizumab in uveitis refractory to other biologic drugs: a study of 3 cases and a literature review. *Clin Exp Rheumatol* 2014;32(4 Suppl 84):S54–S57.
27. Santos-Gómez M, Calvo-Río V, Blanco R, et al. The effect of biologic therapy different from infliximab or adalimumab in patients with refractory uveitis due to Behçet's disease: results of a multicentre open-label study. *Clin Exp Rheumatol* 2016;34(6 Suppl 102):S34–S40.
28. Calvo-Río V, de la Hera D, Blanco R, et al. Golimumab in uveitis previously treated with other anti-TNF-alpha drugs: a retrospective study of three cases from a single centre and literature review. *Clin Exp Rheumatol* 2014;32(6):864–868.
29. Calvo-Río V, Blanco R, Santos-Gómez M, et al. Golimumab in refractory uveitis related to spondyloarthritis. Multicenter study of 15 patients. *Semin Arthritis Rheum* 2016;46(1):95–101.
30. Calvo-Río V, Blanco R, Beltrán E, et al. Anti-TNF-α therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. *Rheumatology* 2014;53(12):2223–2231.
31. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;140(3):509–516.
32. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* 1985;92(4):467–471.
33. Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. *Eye* 2016;30(10):1277–1292.
34. Maleki A, Meese H, Sahawneh H, Foster CS. Progress in the understanding and utilization of biologic response modifiers in the treatment of uveitis. *Expert Rev Clin Immunol* 2016;12(7):775–786.
35. Cho H, Madu A. Etiology and treatment of the inflammatory causes of cystoid macular edema. *J Inflamm Res* 2009;2:37–43.
36. Ogata A, Tanaka T. Tocilizumab for the treatment of rheumatoid arthritis and other systemic autoimmune diseases: current perspectives and future directions. *Int J Rheumatol* 2012;2012:946048.
37. Ortiz-Sanjuán F, Blanco R, Calvo-Rio V, et al. Efficacy of tocilizumab in conventional treatment-refractory adult-onset Still's disease: multicenter retrospective open-label study of thirty-four patients. *Arthritis Rheumatol* 2014;66(6):1659–1665.
38. Loricera J, Blanco R, Hernández JL, et al. Tocilizumab in patients with Takayasu arteritis: a retrospective study and literature review. *Clin Exp Rheumatol* 2016;34(3 Suppl 97):S44–S53.
39. Loricera J, Blanco R, Hernández JL, et al. Tocilizumab in giant cell arteritis: multicenter open-label study of 22 patients. *Semin Arthritis Rheum* 2015;44(6):717–723.
40. Loricera J, Blanco R, Castañeda S, et al. Tocilizumab in refractory aortitis: study on 16 patients and literature review. *Clin Exp Rheumatol* 2014;32(3 Suppl 82):S79–S89.
41. Lin P. Targeting interleukin-6 for noninfectious uveitis. *Clin Ophthalmol* 2015;9:1697–1702.
42. Adán A, Llorenç V, Mesquida M, Pelegrín L. Tocilizumab treatment for recalcitrant uveitic macular edema. *Graefes Arch Clin Exp Ophthalmol* 2013;251(9):2249–2250.
43. Adán A, Mesquida M, Llorenç V, Modesto C. Tocilizumab for retinal vasoproliferative tumor secondary to juvenile idiopathic arthritis-associated uveitis: a case report. *Graefes Arch Clin Exp Ophthalmol* 2014;252(1):163–164.
44. Papo M, Bielefeld P, Vallet H, et al. Tocilizumab in severe and refractory non-infectious uveitis. *Clin Exp Rheumatol* 2014;32(4 Suppl 84):S75–S79.
45. Tappeiner C, Mesquida M, Adán A, et al. Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2016;43(12):2183–2188.
46. Deroux A, Chiquet C, Bouillet L. Tocilizumab in severe and refractory Behcet's disease: four cases and literature review. *Semin Arthritis Rheum* 2016;45(6):733–737.
47. Mesquida M, Leszczynska A, Llorenç V, Adán A. Interleukin-6 blockade in ocular inflammatory diseases. *Clin Exp Immunol* 2014;176(3):301–309.