Accepted Manuscript

Anti-il6-r tocilizumab in refractory and non-infectious uveitic cystoid macular edema. Multicenter study of 25 patients


PII: S0002-9394(19)30003-0
DOI: https://doi.org/10.1016/j.ajo.2018.12.019
Reference: AJOPHT 10790


Received Date: 16 July 2018
Revised Date: 28 December 2018
Accepted Date: 29 December 2018


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ABSTRACT

PURPOSE: Cystoid macular edema (CME) is a leading cause of blindness. In this study we assessed the efficacy and safety of Tocilizumab (TCZ) in refractory CME.

DESIGN: Retrospective case series.

METHODS: Patients with CME secondary to non-infectious uveitis who had inadequate response to corticosteroids and at least one 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± SD 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's 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 microns; p=0.00009) and BCVA (0.39±0.31 vs 0.54±0.33; p=0.0002) 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=0.002) 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.
ANTI-IL6-R TOCILIZUMAB IN REFRACTORY AND NON-INFECTIOUS UVEITIC CYSTOID MACULAR EDEMA. MULTICENTER STUDY OF 25 PATIENTS

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Short title: TCZ in refractory CME
Keywords: Cystoid macular edema, uveitis, anti-TNF therapy, Tocilizumab.
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)(3)(4)(5). Underlying diseases associated with uveitis-related CME are sarcoidosis, juvenile idiopathic arthritis (JIA), birdshot chorioretinopathy and Behçet disease (2)(4). Most uveitis may complicate with CME and blindness, depending on the underlying disease, anatomical pattern and chronicity of inflammation. CME-related blindness has been reported in 5-72% of patients with sarcoid-uveitis (6)(7)(8), 16-22% of patients with JIA-associated uveitis (9)(10)(11) and 25-42% of patients with Behçet disease (12)(13). According to anatomical location, panuveitis (36%-66%) and intermediate 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)(15)(9). 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 biological agents (15), such as monoclonal anti-tumor necrosis factor (anti-TNFα) 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, CA, 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)(20)(21)(22)(23)(24); however, in the STOP-Uveitis Study (25), Sepah et al. reported the primary end-point analyses of the safety and efficacy of two different doses of intravenous infusions of TCZ (4 and 8 mg/kg respectively, every 4 weeks) until month 6 in 37 patients with non-infectious intermediate, posterior or pan-uveitis.

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 non-infectious uveitis-associated CME, refractory to corticosteroids and at least one conventional immunosuppressive drug, and in most cases (n=22) to other biological 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 non-infectious 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. IRB/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/weekly. The primary end-point 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 one conventional synthetic immunosuppressive drug, and a
biological agent (generally an anti-TNFα inhibitor), and had presented partial or no response to these therapies. Only 3 patients received TCZ as the first biological agent.

Macular edema was considered persistent or unresponsive to corticosteroids, to synthetic immunosuppressive drugs or to biological agents when central foveal thickness was ≥300 µm and/or presence of cystic spaces was confirmed after regular evaluations while patients were receiving the abovementioned 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)(27)(28)(29)(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-g 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 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 one-hour intravenous (IV) infusion of 8 mg/kg TCZ was given to 23 of 25 patients at 4-week intervals. One patient with JiA received an IV infusion of 8 mg/kg every 2 weeks, and the patient with sarcoidosis was treated with 162 mg/sc/weekly. 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 anatomical (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 (Carl Zeiss). Scans were obtained using a 512x128 scan pattern.

Intraocular inflammation was assessed according to the Standardization of Uveitis Nomenclature (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 two-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). Results were expressed as the mean +/- SD or median (interquartile range [IQR]) as appropriate. Wilcoxon’s 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 biological agents were enrolled in the study (TABLE 1). Mean age was 33.6±18.9 years. Underlying diseases were JIA (n=9), Behçet’s 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 TCZ**

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/m²/weekly (n=19); cyclosporine A (CsA) 2-5 mg/kg/daily (n=17); azathioprine 1-4 mg/kg/daily (n=2); leflunomide pediatric dose of 10 mg/daily for children weighing 20-40 kg and 20 mg/daily for children weighing >40 kg, and adult dose of 100 mg/daily for three days and then 10-20 mg/daily (n=2); sulfasalazine 2-3 gr/daily (n=1); thalidomide 100-200 mg/daily (n=1); mycophenolate 2-3 g/daily (n=3); acetazolamide 1 gr/daily (n=1); cyclophosphamide 1-2 mg/kg/daily administered orally (n=1).

Most patients had also received other biological agents (Figure 1): adalimumab (ADA) 40 mg sc every 1 or 2 weeks (n=19); etanercept (ETN) 12.5-50 mg/sc/weekly (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) a single course of 2 doses of 1 gr iv 2 weeks apart (n=2); golimumab (GLM) 50 mg/sc/monthly (n=2); daclizumab 1-2 mg/kg every 2 or 4 weeks (n=1), and anakinra 100 mg/sc/daily (n=1).

**Outcome variables after TCZ 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 vs 259.1±49.5 microns; p<0.0001) 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 two-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 (91%) of 23 eyes 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 (70.3%) of 27 eyes affected at baseline. Mean BCVA improved from 0.39±0.31 at baseline to 0.54±0.33 (p<0.0001) at month 12 (Figure 3). Mean prednisone dose was reduced from 15.9±13.6 mg/daily at baseline to 3.1±2.3 mg/daily at month 12 (p=0.002). 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 biological 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 sequel of retinal 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 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)(38)(39)(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)(20)(21)(22)(23)(26)(42)(43)(44)(45)(46)(47).

The most frequent causes of non-infectious CME secondary to inflammatory diseases are HLA-B27 positive anterior uveitis, JIA, intermediate uveitis (due to sarcoidosis, multiple sclerosis, and pars-planitis), posterior uveitis (in systemic diseases, such as sarcoidosis and Behçet’s 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 due 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 anatomical 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 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 (17), which may play a key role in increasing blood-retinal barrier permeability and disruption (16). The up-regulation 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 et al. in 2011 (23). In 2014, the study by Papo et al. (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 two patients who did not respond (44) 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.

In the last two years, two remarkable studies have been published by Mesquida et al. (24) and by Sepah et al. (25). Mesquida et al. (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 chorioretinopathy, 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 biological agents. The dose of TCZ for CME most frequently used is 8 mg/kg iv every 4 weeks (18)(19)(20)(21)(22)(26)(44).

The improvement of CME after month 24 of TCZ therapy was highly significant. The study by Sepah et al. (25) presents the largest series, with a total of 37 patients. The underlying inflammatory diseases were: sarcoidosis, Vogt-Koyanagi-Harada syndrome, birdshot chorioretinopathy, punctate inner choroiditis, Behçet disease, tubulointerstitial nephritis and uveitis (TINU syndrome), and idiopathic 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 either TCZ at a dose of 4 mg/kg or of 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 chorioretinopathy, 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, acetzolamide and cyclophosphamide) and biological therapies (adalimumab, etanercept, infliximab, abatacept, rituximab, golimumab, daclizumab and anakinra); in one patient, five different biological 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 et al., TCZ was used in monotherapy, with a prior washout period of 3 months. The study by Sepah et al. 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 et al., 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/weekly. 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-TNFα 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.
ACKNOWLEDGEMENTS/DISCLOSURES:

A. Funding/Support: The study was partially supported by RETICS Programs, RD08/0075 (RIER) and RD12/0009/0013 from “Instituto de Salud Carlos III” (ISCIII) (Spain).

B. Financial Disclosures:

- Dr. Nuria Vegas-Revenga, MD; received grants/research supports from AbbVie, Roche, Pfizer, Lilly, Gebro Pharma, MSD, Novartis, Bristol-Myers, Janssen and Celgene. Dr. Vanesa Calvo- Río MD, PhD; received grants/research supports from MSD and Roche, and had consultation fees/participation in company sponsored speaker’s bureau from AbbVie, Lilly, Celgene, Grünenthal and UCB pharma. Dr. Marina Mesquida, MD, PhD; is currently employed by Hoffmann-La Roche Ltd, Basel, Switzerland. Dr. Alfredo Adán, MD, PhD; had advisory boards, lectures and grants from AbbVie. Dr. David Díaz-Valle, MD, PhD; had consultation fees/participation in company sponsored speaker’s bureau from AbbVie, MSD, Allergan, Bausch & Lomb and Thea. Dr. Lucía Martínez-Costa MD, PhD; received grants/research supports from Abbvie and Allergan, and had consultation fees/participation in company sponsored speaker’s bureau from Abbvie. Dr. Inmaculada Calvo MD, PhD received grants/research support from Abbvie, Novartis, Pfizer, Roche, Sanofi, Clementia, and had consultation fees/participation in company sponsored speaker’s bureau from Abbvie, Roche, Novartis. Dr. Antonio Atanes, MD; had consultation fees/participation in company sponsored speaker’s bureau from Abbott, MSD, Menarini, Gebro, Grünenthal, Roche, Pfizer, Novartis, Celgene, Bristol Myers Squibb and Lácer. Dr. Miguel Cordero, MD; received lecture grants from AbbVie, Merck, Sharp & Dohme, Allergan, UCB; had advisory boards from Abbvie, Allergan, Alimera; and travel grants from Abbvie, UCB, Allergan, Novartis. Dr. LC Domínguez-Casas, MD; received grants/research supports from Celgene, Sanofi, Roche, Novartis, Lilly, Pfizer and Janssen. Dr. Belén Atienza-Mateo, M.D; had received grants/research supports from Roche, Celgene and GSK. Dr. José Luis Martín-Varillas received grants/research supports from AbbVie, Pfizer and Celgene. Dr. Javier Loricera, MD; received fees for presentations sponsored by Novartis and Roche and had attended to congresses thanks to the economic support of Novartis, Roche, MSD, Abbvie, Lilly, Pfizer, Celgene, Janssen and Gebro Pharma. Dr. Miguel A González-Gay, MD, PhD; received grants/research supports from Abbott, MSD and Roche, and had consultation fees/participation in company sponsored speaker’s bureau from Abbott, Pfizer, Roche, Novartis, MSD, Lilly and Sanofi. Dr. Ricardo Blanco, MD, PhD; received grants/research supports from Abbott, MSD and Roche, and had consultation fees/participation in company sponsored speaker’s bureau from Abbott, Pfizer, Roche, Bristol-Myers, Janssen and MSD.

No financial disclosure declared: María Victoria Hernández, MD, PhD; Emma Beltrán, MD; Elia Valls Pascual, MD; Gisela Díaz-Cordovés, MD; Marisa Hernández-Garfella, MD; Luis F Linares, MD; Consuelo Modesto, MD; Carmen González-Vela, MD, PhD; Rosalia Demetrio- Pablo, MD, PhD; Elena Aurrecoechea, MD, PhD; Natalia Palmou-Fontana, MD, PhD; J.L. Hernández, MD, PhD.
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*Prof. MA González-Gay, Dr. JL Hernández and Dr. R Blanco shared senior authorship.
*This study was presented in part at the 2017 American College of Rheumatology Congress held in San Diego, CA.

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FIGURE CAPTIONS:

Figure 1. Flow-chart showing the biologic therapy used in 25 patients with refractory CME-associated uveitis that required TCZ.

Footnote: Abbreviations: ADA, adalimumab; CANA, canakinumab; ETN, etanercept; GLM, golimumab; IFX, infliximab; TCZ, tocilizumab.

( ): number of cases.

Figure 2: Top- Time course of macular thickness during the study (affected eyes). Bars represent mean and standard error.

Footnote: *p<0.001.

Bottom- Macular thickness: Improvement following tocilizumab therapy for each underlying disease.

Footnote: *p<0.05

Figure 3. Mean changes of best corrected visual acuity (BCVA) after TCZ therapy (affected eyes). Bars represent mean and standard error.

Footnote: * p<0.001
**Table 1.** Baseline main general features of the 25 patients with refractory and severe uveitic CME.

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

**Abbreviations** (in alphabetical order): 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.
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Table 2. Literature review of studies of patients with refractory uveitis-related CME treated with TCZ.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with CME</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Sex, (W/M), n</td>
<td>2/0</td>
<td>5/0</td>
<td>1/0</td>
<td>1/0</td>
<td>2/0</td>
<td>7/0</td>
<td>NS</td>
<td>10/0</td>
<td>3/2</td>
<td>10/2</td>
</tr>
<tr>
<td>Age, years</td>
<td>27-69</td>
<td>30-68</td>
<td>56</td>
<td>29</td>
<td>21-47</td>
<td>23-70</td>
<td>7-30</td>
<td>23</td>
<td>23-57</td>
<td>15-62</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>BSRC and idiopathic uveitis</td>
<td>BSRC (n=3), JIA (n=1), idiopathic panuveitis (n=1)</td>
<td>Spondyloarthritis (n=1), idiopathic panuveitis (n=1)</td>
<td>BSRC (n=3), JIA (n=3), idiopathic uveitis (n=1)</td>
<td>JIA</td>
<td>BSRC</td>
<td>JIA (n=2), ankylosing spondylitis (n=1), rheumatoid arthritis (n=2)</td>
<td>JIA (n=6), BSRC (n=2), idiopathic panuveitis (n=2), sympathetic ophthalmia (n=1), ankylosing spondylitis (n=1)</td>
<td>BSRC (n=2), sarcoidosis (n=2), Behçet disease (n=1), Vogt-Koyanagi-Harada syndrome (n=2), Panularte Inner Choroiditis (n=1), TINU syndrome (n=1); idiopathic uveitis (n=4)</td>
<td>JIA (n=9), BSRC (n=4), sarcoidosis (n=1), Behçet disease (n=7), idiopathic uveitis (n=4)</td>
</tr>
<tr>
<td>Uveitis pattern</td>
<td>Posterior uveitis + CME, Vitritis + vasculitis + CME.</td>
<td>Uveitis-related CME</td>
<td>Severe bilateral CME</td>
<td>JIA-associated uveitis complicated with CME and VPRT</td>
<td>Panuveitis + CME</td>
<td>Posterior uveits+CME (n=6) and panuveits + CME (n=1)</td>
<td>JIA-associated anterior uveitis complicated with CME</td>
<td>Posterior uveits + CME</td>
<td>Chronic anterior uveitis + CME (n=3), acute anterior uveitis + CME (n=1), intermediate uveitis + CME (n=1), ME with quiescent uveitis</td>
<td>Intermediate uveits (n=6), posterior uveits (n=5), panuveits (n=28).</td>
</tr>
<tr>
<td>Previous treatment</td>
<td>MTX, AZA, MMF, ADA</td>
<td>MTX, AZA, CYC, ADA</td>
<td>MTX, AZA, IFX, ADA</td>
<td>MTX, CSa, IFX, ADA</td>
<td>MTX, CSa, IFX, ADA</td>
<td>MTX, CSa, IFX, ADA</td>
<td>MTX, CSa, MMF, LFN, ADA, IFN, ADA, ABA, ANK</td>
<td>MTX, AZA, CSa, ADA, IFN, ADA, ABA, RTX</td>
<td>MTX, AZA, CSa, IFN, ADA, ABA, ANK</td>
<td>MTX, MMF, CSa, ADA, IFN, ADA, ETN, ABA, GLM</td>
</tr>
<tr>
<td>TCZ regimen</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg every 4 weeks</td>
<td>8 mg/kg/ every 4 weeks (n=23), 8 mg/kg/ every 2 weeks (n=1), 162 mg/kg/ every week (n=1)</td>
<td></td>
</tr>
<tr>
<td>Adverse effects related to TCZ</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Grade 1 neutropenia (n=1) and community-acquired pneumonia (n=1)</td>
<td>Neutropenia (n=2)</td>
<td>Nausea (n=1), viral conjunctivitis and bullous impetigo (n=1).</td>
</tr>
<tr>
<td>Months of TCZ treatment</td>
<td>6-8</td>
<td>6-12</td>
<td>6</td>
<td>12</td>
<td>7-25</td>
<td>12-18</td>
<td>3-12</td>
<td>4-35</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Ocular outcome</td>
<td>Improvement (n=2)</td>
<td>Improvement (n=5)</td>
<td>Inactive</td>
<td>Improvement (n=2)</td>
<td>Improvement (n=5)</td>
<td>Inactive</td>
<td>Improvement (n=5)</td>
<td>Inactive (n=12)</td>
<td>Improvement (n=37)</td>
<td>Inactive (n=14)</td>
</tr>
</tbody>
</table>

Abbreviations (in alphabetical order): ABA= abatacept, Acet= Acetazolamide, ADA= adalimumab, AZA = azathioprine, BSRC= birdshot retinochoroidopathy, CME= cystoid macular edema, CsA= cyclosporine A, CYC= cyclophosphamide, DCZ= daclizumab, ETN-etanercept, GOLM= golimumab, HCQ= Hydroxychloroquine, IFN= interferon alpha, IFX= infliximab, IVIG= intravenous immunoglobulin, JIA= juvenile idiopathic arthritis, LFN= Leflunomide, MMF= mycophenolate mofetil, MTX= methotrexate, NS= not specified, RTX= rituximab, TCZ= tocilizumab, TINU Syndrome= Tubulointerstitial nephritis and uveitis, VPRT= Retinal vasoproliferative tumor.
Figure 1.
Figure 2 Top.

Figure 2 Bottom.
Figure 3.
Cystoid macular edema secondary to non-infectious uveitis is a leading cause of blindness. Twenty-five patients with inadequate response to corticosteroids and at least one conventional immunosuppressive drug were selected to receive treatment with Tocilizumab. After 12 months of therapy a statistically significant improvement in macular thickness and best corrected visual acuity was obtained with minor side effects.