Tocilizumab in Behçet's disease with refractory ocular and/or neurological involvement: response according to different clinical phenotypes

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ABSTRACT

Objective. *Anti-IL6R tocilizumab (TCZ) therapy has proved to be useful in the treatment of refractory ocular and/or neurological involvement of Behçet's disease (BD). However, TCZ efficacy in other BD manifestations remains unclear. In this study we aimed to assess the efficacy of TCZ in the different clinical phenotypes of BD.*

Methods. *This is a multicentre study of BD patients treated with TCZ, due to refractivity to standard systemic treatment.*

Results. *We studied 16 patients (10 men/6 women); mean age 36.5±18.2 years. The main clinical manifestations at TCZ onset were ocular, oral and/or genital ulcers, arthritis, folliculitis and/or neurological involvement. Before TCZ, they had received several conventional and/or biological immunosuppressants, such as methotrexate, cyclosporine, adalimumab or infliximab. TCZ was used in monotherapy or combined with conventional immunosuppressive drugs. The main indications for TCZ prescription were refractory uveitis (n=14) and refractory neurobehçet (n=2). After a median [IQR] follow-up of 20 [9-45] months using TCZ, neurological and ocular domains improved in most cases with complete remission in most patients with uveitis. Articular and peripheral venous manifestations also experienced a favourable evolution. However, oral/genital ulcers, skin lesions and intestinal manifestations followed a torpid course.*

Conclusion. *TCZ is effective in BD with major clinical involvement. However, it does not seem to be effective in oral/genital ulcers or skin lesions.*

Introduction

Behçet's disease (BD) is an idiopathic variable vessel vasculitis with a chronic course and potential involvement of multiple organs (1, 2). The clinical spectrum of BD includes mucocutaneous, ocular, gastrointestinal, articular, neurological and vascular manifestations. Since it is not a uniform disorder, some experts prefer to consider this entity as a syndrome rather than a unique disease. In this sense, different phenotypes of BD have been described according to the predominant symptom. To date, the major phenotypes recognised are the mucocutaneous and articular phenotype, the extra-parenchymal neurological and peripheral vascular phenotype and the parenchymal neurological and ocular phenotype.

Anti-interleukin 6 receptor (IL-6 R) tocilizumab (TCZ) therapy has demonstrated efficacy in the treatment of ocular manifestations of BD, in particular in cases refractory to conventional and/or biological therapies (4-6). TCZ has also shown favourable results in refractory neurological (7, 8), vascular (9) and intestinal (10) involvement of BD. However, the response of other manifestations to this therapy remains unclear.

In this study we aimed to assess the efficacy of TCZ in the different clinical phenotypes of BD.

Patients and methods

Design and enrolment criteria

We conducted an observational national multicentre retrospective study of TCZ therapy in patients diagnosed with BD refractory to standard systemic immunosuppressive treatment, in-

cluding biological therapy. All patients fulfilled the proposed International Criteria for BD (11). Rheumatology, Autoimmune Diseases or Uveitis Units of 9 referral Spanish hospitals collaborated in the recruitment of the patients. Uveitis was anatomically classified according to the Standardization of Uveitis Nomenclature (SUN) Working Group (12). The presence and degree of intraocular inflammation, vitritis, retinal vasculitis, macular thickening and impaired visual acuity were assessed as previously described (5). Neurobehçet was considered to be present when there were symptoms and signs of parenchymal or non-parenchymal neurological involvement and there was no evidence of other organic causes, according to our previous experience and the international consensus recommendations for diagnosis and management of neuroBehçet's disease (13-15). Patients with ocular and/or neurological involvement were followed by Rheumatologists in close collaboration with specialised Ophthalmologists and/or Neurologists, respectively.

Malignancy or systemic infectious diseases, including latent tuberculosis, hepatitis B or hepatitis C infection, were excluded before TCZ onset, following the Spanish National Guidelines as described in former reports (4, 5, 16). If latent tuberculosis was present, prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biologic agent and maintained for 9 months.

TCZ was prescribed as an off-label indication and, therefore, written informed consent was requested and obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee (NVR-2018.124).

Patients were treated with TCZ at standard dose of 8 mg/kg/i.v./4 weeks or 162 mg/s.c./weekly in monotherapy or combined with conventional immunosuppressive drugs.

Outcome variables

The response to TCZ of the different phenotypes was described as improvement or non-improvement for every manifestation at the end of follow-up of each patient. For the first condition, complete or partial response were considered when there was a definite or incomplete resolution of signs or symptoms at the end of follow-up of each patient, respectively. Remission was defined as the presence of inactive disease for at least 3 months. Progressive or relapsing symptoms, as well as stability of the disease, were acknowledged as non-improvement. Regarding uveitis, complete response was defined as a decrease to grade 0 in the level of inflammation for anterior uveitis and vitritis along with inactive retinal vasculitis, significant decrease of macular thickening and improvement of best corrected visual acuity.

Statistical analysis

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

Results

Demographic and clinical data at TCZ onset

A total of 16 patients (10 men/ 6 women) with refractory BD were studied. The mean age was 36.5±18.2 years, and 12 patients (75%) were HLA-B51 positive. All patients had ocular manifestations (12 bilateral and 4 unilateral), with a sum of 28 affected eyes. The different uveitis patterns were the following: panuveitis (n=11; 5 with retinal vasculitis), anterior (n=3) and posterior (n=2) uveitis. In addition, 9 patients had cystoid macular oedema. Other BD manifestations at TCZ onset were: oral/genital ulcers (n=10, 3 patients with only oral ulcers), arthritis (n=7), folliculitis (n=5), neurological involvement (n=5), erythema nodosum (n=3), deep venous thrombosis (n=1) and/or intestinal vasculitis (n=1). Demographic and clinical characteristics of the patients are shown in Table I. The median (IQR) duration of disease at the time patients first received TCZ was of 32 (18–114) months.

Treatment before TCZ

Besides glucocorticoids, all patients had received several conventional immunosuppressive drugs: methotrexate (MTX) (n=13), cyclosporine A (CsA) (n=8), azathioprine (AZA) (n=6), cyclophosphamide (n=3) and/or mycophenolate mofetil (MMF) (n=1). Additionally, all but two patients had received the following biologic agents: adalimumab (n=10), infliximab (n=7), golimumab (n=3), canakinumab (n=1), certolizumab pegol (n=1) and/or etanercept (n=1). Also, 3 patients had received treatment with colchicine (n=3) and/or thalidomide (n=1). Individual therapies are shown in Table I.

Therapy with TCZ and outcome of the different phenotypes

The main indications for TCZ administration were refractory uveitis in 14 patients and refractory neuroBehçet in the remaining 2 patients (one of them with right hemiparesis and a cranial magnetic resonance that showed signs of left pseudotumour and demyelinating lesions with lymphocytic pleocytosis of the cerebrospinal fluid, and another with vascular migraine and axonal sensory polyneuropathy of her upper and lower limbs confirmed by electromyography).

TCZ was used in monotherapy in 8 patients or combined with conventional immunosuppressive drugs in 8 other patients (MTX in 3, AZA in 3, MMF in 1 and CsA in 1). TCZ was given at the standard intravenous dose (8 mg/kg/4 weeks) in 13 patients or subcutaneously (162 mg/week) in the remaining 3 patients.

After a median (IQR) follow-up of 20 (9-45) months using TCZ, most patients experienced ocular improvement (13/16, 81.25%), with complete remission in 10 (62.5%). Evolution of ocular parameters is shown in Figure 1.

Regarding the 5 patients with neurological manifestations, 3 (60%) reached a complete remission (2 patients with optic neuritis and 1 patient with right hemiparesis). A patient who suffered a stroke that was attributed to BD had a

Table I. Demographic and clinical characteristics of patients with Behçet's disease receiving tocilizumab therapy.

Case	Sex/ age	Indication of TCZ	Combined therapy	Uveitis pattern	Neurobehçet	Oral/ genital ulcers	Articular	Cutaneous	Other (vascular, intestinal)	Follow-up	Previous therapy
1	M/ 27	Uveitis	MTX	Posterior+CME ↑						60	MTX, CsA, CFM
2	F/ 42	Uveitis		Panuveitis+CME ↑		Orogenital ↔		EN ↔		1	MTX, CsA, CFM, AZA, ADA, GLM
3	M/ 50	Uveitis		Panuveitis+CME ↑	Optic neuritis ↑		Arthritis ↑			48	MTX, CsA, ADA, GLM
4	M/ 35	Uveitis		Panuveitis,+ RV ↑		Oral ↔		Folliculitis ↔		12	MTX, CsA, AZA, MMF, IFX
5	F/ 67	Uveitis		Panuveitis+CME +RV ↑						16	MTX, CsA, ADA, IFX
6	M/ 31	Uveitis		Panuveitis+CME+RV ↑		Orogenital ↔		Folliculitis ↔		6	MTX, CsA, ADA
7	F/ 22	Uveitis	CsA	Panuveitis+CME+RV ↑						3	MTX, CsA, ADA
8	M/ 75	Uveitis		Panuveitis+CME+RV ↑		Orogenital ↔	Arthritis ↑	Folliculitis ↔		24	MTX, CsA, ADA
9	M/ 10	Uveitis		Anterior ↑	Hemorrhagic stroke ↔	Orogenital ↑		EN ↑		12	CANA, ETN
10	F/ 48	Uveitis + arthritis	MTX	Anterior ↑		Orogenital ↔	Arthritis ↔	EN, folliculitis ↔		26	MTX, Colchicine, IFX, ADA, GLM
11	M/ 16	Uveitis +neurobehçet	AZA	Panuveitis ↑	Optic neuritis ↑	Oral ↔	Arthritis ↔			42	AZA, ADA, IFX
12	F/ 48	Uveitis + arthritis	MTX	Panuveitis ↔		Oral ↔	Arthritis ↑			13	MTX, ADA, IFX
13	M/ 35	Uveitis	MMF	Panuveitis ↔						3	MTX, ADA
14	M/ 66	Uveitis	AZA	Anterior ↑						38	IFX
15	M/ 45	Neurobehçet	AZA	Panuveitis ↑	Right hemiparesis ↑	Orogenital ↑	Arthritis ↑		Deep venous hrombosis ↑	64	Colchicine, MTX, AZA
16	F/39	Neurobehçet		Posterior ↔	ASP, vascular migraine ↔	Orogenital ↔	Arthritis ↔	Folliculitis ↔	Intestinal vasculitis ↔	96	Colchicine, Thalidomide, MTX, AZA, CFM, IFX, ADA

↑: improvement; ↔ : no improvement; ASP: axonal sensory polyneuropathy; AZA: azathioprine; CANA: canakimumab; CME: cystoid macular oedema; CsA: cyclosporine A; GLM: golimumab; EN: erythema nodosum; F: feminine; M: masculine; MMF: mycophenolate mofetil; MTX: methotrexate; RV: retinal vasculitis; TCZ: tocilizumab.
Age is expressed in years and follow-up in months.

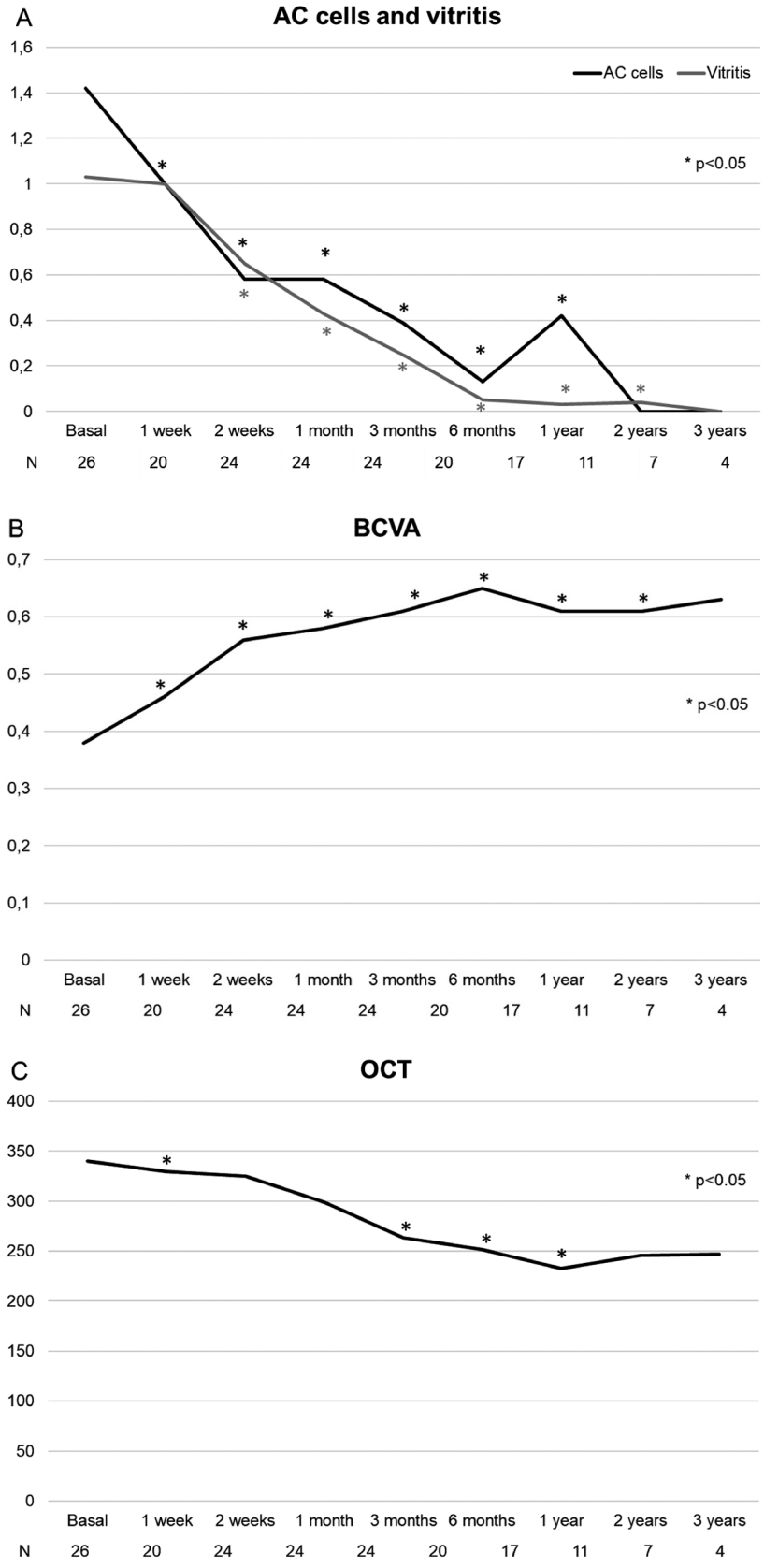

Fig. 1. Evolution of ocular parameters with tocilizumab therapy.
A: Anterior Chamber (AC) cells and vitritis. **B:** Best-corrected visual acuity (BCVA). **C**: Macular thickness measured in μm by optical coherence tomography (OCT). Data are expressed as mean values and compared with basal results. N represents the number of eyes with available data at each point of assessment.

stable course. Another with axonal sensory polyneuropathy and vascular migraine suffered an infusion reaction, so the effect of anti-IL6 R could not be adequately evaluated. However, TCZ was effective in only 2/10 patients with oral/genital ulcers. Articular manifestations improved in 4/7 patients (57.14%), with complete remission of arthritis in 2 of them. The outcome of the different BD phenotypes with TCZ therapy is individually described in Table I and shown graphically in Figure 2.

TCZ had to be withdrawn temporarily in 1 case, due to an episode of cellulitis with sepsis, and permanently in 4 cases, due to a severe infusion reaction, arthritis impairment, persistence of oral ulcers or relapsing uveitis (1 each).

Discussion

This study shows the experience with TCZ in highly refractory BD patients with different clinical manifestations. The results suggest that TCZ is effective in ocular and neurological phenotypes, whereas the mucocutaneous phenotype presents a torpid response and other manifestations have a variable evolution.

IL-6 is a pleiotropic proinflammatory cytokine that induces hepatic hepcidin and acute phase reactant production and B and T lymphocytes differentiation, among other actions. IL-6 is also implicated in the development of cardiovascular diseases. Increased concentrations of IL-6 have been detected in the vitreous fluid of patients with chronic uveitis (17) as well as in the cerebrospinal fluid of patients with BD (18-20).

TCZ is a humanised monoclonal antibody against soluble and membrane-bound IL-6 R, which has been approved for the treatment of rheumatological conditions, such as rheumatoid arthritis, giant cell arteritis and systemic and polyarticular juvenile arthritis (www.fda.gov, www.ema.europa.eu). TCZ has also shown efficacy in patients with refractory ocular inflammatory diseases (4-6, 16, 21). Moreover, it has been successfully used in critical cases of Coronavirus disease 2019 (22). However, the indication of TCZ for the treatment of BD has not yet been standardised.

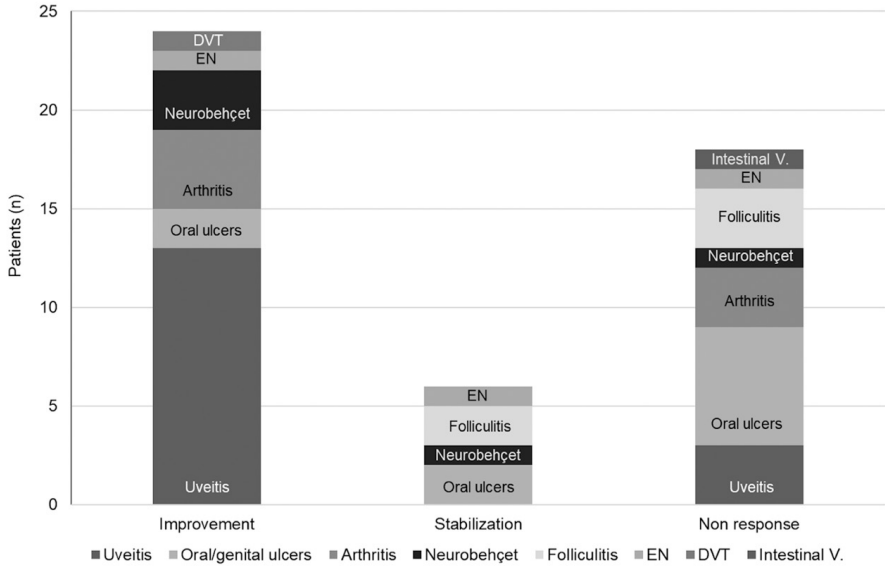

Fig. 2. Outcome of the different Behçet's disease phenotypes.
DVT: deep venous thrombosis; EN: erythema nodosum; V: vasculitis.

Nowadays, there is a growing evidence on the existence of different phenotypes of BD with distinct clinical patterns and subsequent diverse therapeutic response (3, 23). To date, there are 3 major phenotypes recognised: the mucocutaneous and articular phenotype, the extra-parenchymal neurological and peripheral vascular phenotype and the parenchymal neurological and ocular phenotype. Different treatment strategies have been proposed according to the predominant BD manifestations/phenotype (2, 23-26).

However, to the best of our knowledge, the experience with TCZ therapy according to the different BD phenotypes is scarce. In this regard, Akiyama *et al*. have recently published a systematic literature review on TCZ effectiveness in BD (27). Although they did not provide information on new patients, they reviewed 20 articles that together included 47 BD patients treated with TCZ. The clinical manifestations at TCZ onset were: oral/genital ulcers (n=21), skin (n=14), articular (n=11), gastrointestinal (n=4), ocular (n=25), neurological (n=6), vascular (n=7) involvement and secondary amyloidosis (n=2). All of them were refractory to conventional immunosuppressive therapy and/or biologic agents. They concluded that TCZ may be effective and serve as an alternative treatment for refractory ocular, neurological, and vascular BD manifestations, as well as for secondary amyloidosis, but not for patients with mucocutaneous and joint involvement. Based on our own experience in a series of Spanish patients with BD refractory to conventional and biological therapies, we support the efficacy of TCZ in those individuals with predominant ocular and / or neurological involvement. In line with these observations, Shapiro *et al*. published the first report of administration of TCZ for the treatment of a 30-year-old man with highly refractory uveitis and recurrent meningoencephalitis due to neurobehçet, with a successful response (7). Addimanda *et al*. also reported a sustained response to TCZ of 3 patients with severe neurobehçet who did not respond to conventional immunosuppressants including anti-TNF-α drugs (8).

As stated by Akiyama *et al*. in their review (27), in our series cutaneous and joint manifestations showed a variable evolution and oral/genital ulcers had a torpid course following TCZ. This could be in part explained by the critical role of IL-6 in epithelial cell homeostasis and cutaneous wound healing (28), whose IL-6 R inhibition may cause mucocutaneous impairment.

The present study may be somehow limited due to its retrospective nature. In this sense, information on activity disease scores such as the Behçet's Disease Current Activity Form (BDCAF) was not included in this report as it was not performed in most patients.

In our study TCZ was overall well tolerated with no new safety alarms detected. It should be noted that all patients had previously received several immunosuppressants, so we do not know if TCZ could have shown greater efficacy in more patients if it had been administered earlier in the course of the disease.

In conclusion, our study supports the efficacy of TCZ in refractory BD with major clinical involvement.

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Competing interests

V. Calvo-Río had consultation fees/participation in company sponsored speaker's bureau from Abbvie, Lilly, MSD, UCB Pharma and Celgene. M.Á. González-Gay received grants/research support from Abbott, MSD and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbott, Pfizer, Roche and MSD. R. Blanco received grants/research support 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. The other co-authors have declared no competing interests.

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References

1. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
2. HATEMI G, SEYAHI E, FRESKO I *et al*.: One year in review 2019: Behçet's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 121): S3-17.
3. SEYAHI E: Phenotypes in Behçet's syndrome. *Intern Emerg Med* 2019; 14: 677-89.
4. 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 (Suppl. 84): S54-7.

5. ATIENZA-MATEO B, CALVO-RÍO V, BELTRÁN E *et al*.: Anti-interleukin 6 receptor tocilizumab in refractory uveitis associated with Behçet's disease: multicentre retrospective study. *Rheumatology* 2018; 57: 856-64.
6. VEGAS-REVENGA N, CALVO-RÍO V, MESQUIDA M *et al*.: Anti-IL6-receptor tocilizumab in refractory and noninfectious uveitic cystoid macular edema: multicenter study of 25 patients. *Am J Ophthalmol* 2019; 200: 85-94.
7. SHAPIRO LS, FARRELL J, BORHANI HAGHIGHI A: Tocilizumab treatment for neuro-Behçet's disease, the first report. *Clin Neurol Neurosurg* 2012; 114: 297-8.
8. ADDIMANDA O, PIPITONE N, PAZZOLA G *et al*.: Tocilizumab for severe refractory neuro-Behçet: three cases IL-6 blockade in neuro-Behçet. *Semin Arthritis Rheum* 2015; 44: 472-5.
9. DING Y, LI C, LIU J *et al*.: Tocilizumab in the treatment of severe and/or refractory vasculo-Behçet's disease: a single-centre experience in China. *Rheumatology* 2018; 57: 2057-9.
10. CHEN J, CHEN S, HE J: A case of refractory intestinal Behçet's disease treated with tocilizumab, a humanised anti-interleukin-6 receptor antibody. *Clin Exp Rheumatol*. 2017; 35 (Suppl. 108): S116-8.
11. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; 335: 1078-80.
12. 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: 509-16.
13. GONZÁLEZ-GAY MA, GARCÍA-PORRÚA C, BRAÑAS F *et al*.: Epidemiologic and clinical aspects of Behçet's disease in a defined area of Northwestern Spain, 1988-1997. *J Rheumatol* 2000; 27: 703-7.
14. GONZÁLEZ-GAY MA, FERNÁNDEZ CAMBLOR B, SÁNCHEZ-ANDRADE A *et al*.: Behçet syndrome and peripheral neuropathy as a possible new minor criterion. *Rev Clin Esp* 1991; 189: 154-5.
15. KALRA S, SILMAN A, AKMAN-DEMIR G *et al*.: Diagnosis and management of Neuro-Behçet's disease: international consensus recommendations. *J Neurol*. 2014; 261: 1662-76.
16. SÁNCHEZ-BILBAO L, MARTÍNEZ-LÓPEZ D, REVENGA M *et al*.: Anti-IL-6 receptor tocilizumab in refractory Graves' orbitopathy: national multicenter observational study of 48 patients. *J Clin Med* 2020; 9: E2816.
17. LIN P: Targeting interleukin-6 for noninfectious uveitis. *Clin Ophthalmol* 2015; 9: 1697-702.
18. WANG CR, CHUANG CY, CHEN CY: Anticardiolipin antibodies and interleukin-6 in cerebrospinal fluid and blood of Chinese patients with neuro-Behçet's syndrome. *Clin Exp Rheumatol* 1992; 10: 599-602.
19. HIROHATA S, TANIMOTO K, ITO K: Elevation of cerebrospinal fluid interleukin-6 activity in patients with vasculitides and central nervous system involvement. *Clin Immunol Immunopathol* 1993; 66: 225-9.
20. AKMAN-DEMIR G, TÜZÜN E, IÇÖZ S *et al*.: Interleukin-6 in neuro-Behçet's disease: association with disease subsets and long-term outcome. *Cytokine* 2008; 44: 373-6.
21. SILPA-ARCHA S, ORAY M, PREBLE JM *et al*.: Outcome of tocilizumab treatment in refractory ocular inflammatory diseases. *Acta Ophthalmol* 2016; 94: e400-6.
22. GONZÁLEZ-GAY MA, MAYO J, CASTAÑEDA S *et al*.: Tocilizumab: from the rheumatology practice to the fight against COVID-19, a virus infection with multiple faces. *Expert Opin Biol Ther* 2020; 20: 717-23.
23. BETTIOL A, HATEMI G, VANNOZZI L *et al*.: Treating the different phenotypes of Behçet's syndrome. *Front Immunol* 2019; 10: 2830.
24. HATEMI G, CHRISTENSEN R, BANG D *et al*.: 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; 77: 808-18.
25. LECCESE P, OZGULER Y, CHRISTENSEN R *et al*.: Management of skin, mucosa and joint involvement of Behçet's syndrome: A systematic review for update of the EULAR recommendations for the management of Behçet's syndrome. *Semin Arthritis Rheum* 2019; 48: 752-62.
26. ESATOGLU SN, HATEMI G: Update on the treatment of Behçet's syndrome. *Intern Emerg Med* 2019; 14: 661-75.
27. AKIYAMA M, KANEKO Y, TAKEUCHI T: Effectiveness of tocilizumab in Behçet's disease: A systematic literature review. *Semin Arthritis Rheum* 2020; 50: 797-804.
28. JOHNSON BZ, STEVENSON AW, PRÊLE CM *et al*.: The Role of IL-6 in Skin Fibrosis and Cutaneous Wound Healing. *Biomedicines* 2020; 8: 101.