




# Tocilizumab in Behçet Disease: A Multicenter Study of 30 Patients

Mohamed-Yacine Khitri<sup>1</sup> , Alessandra Bartoli<sup>1</sup>, Georgina Maalouf<sup>1</sup>, Alban Deroux<sup>2</sup>, Carlo Salvarani<sup>3</sup>, Giacomo Emmi<sup>4</sup>, Omer Karadag<sup>5</sup> , Gerard Espinosa<sup>6</sup> , Mathilde Leclercq<sup>7</sup>, Gabriele Simonini<sup>8</sup>, Mathieu Vautier<sup>1</sup>, Patrice Cacoub<sup>1</sup>, and David Saadoun<sup>1</sup>

**ABSTRACT. Objective.** To evaluate tocilizumab (TCZ) efficacy in patients with refractory Behçet disease (BD).

**Methods.** This is a multicenter study of 30 patients fulfilling the international criteria for BD and treated with TCZ at different European referral centers. The clinical response was evaluated at 6 months from TCZ initiation.

**Results.** Ninety percent of patients with BD were refractory or intolerant to anti-tumor necrosis factor (anti-TNF) agents. Overall, TCZ was effective in 25 (83%) patients with BD of whom 18 (60%) and 7 (23%) were complete and partial responders, respectively. The complete response was 67%, 60%, and 42% in patients with uveitis (18/30), neurological manifestations (5/30), and mucocutaneous and/or articular (7/30) manifestations, respectively. TCZ had a significant steroid-sparing effect allowing patients to decrease their median daily prednisone dose from 20 (IQR 10-40) mg/day to 9 (IQR 5-13) mg at 6 months ( $P < 0.001$ ). The number of patients with BD needing concomitant disease-modifying antirheumatic drug therapy fell from 7 (23%) to 4 (13%) at 6 months. Mild to moderate side effects were observed in 6 (20%) patients, and 3 (10%) presented with serious adverse events (pneumonia, intestinal perforation, and septicemia) requiring therapy discontinuation in 2 cases.

**Conclusion.** TCZ seems to be an effective alternative to anti-TNF agents in treating BD-related uveitis and neurological manifestations.

*Key Indexing Terms:* Behçet disease, neuro-Behçet, tocilizumab, uveitis

<sup>1</sup>M.Y. Khitri, MD, A. Bartoli, MD, G. Maalouf, MD, M. Vautier, MD, P. Cacoub, MD, PhD, D. Saadoun, MD, PhD, Department of Internal Medicine and Clinical Immunology France, Centre National de Référence Maladies Autoimmunes Systémiques Rares, Centre National de Référence Maladies Autoinflammatoires et Amylose, and Inflammation-Immunopathology-Biotherapy Department (DMU i3), Sorbonne Université, AP-HP, Hôpital Pitié Salpêtrière, Paris, France; <sup>2</sup>A. Deroux, MD, Department of Internal Medicine, University Hospital of Grenoble, Grenoble, France; <sup>3</sup>C. Salvarani, MD, PhD, Division of Rheumatology, Azienda USL-IRCCS di Reggio Emilia, University of Modena and Reggio Emilia, Modena and Reggio Emilia, Italy; <sup>4</sup>G. Emmi, MD, PhD, Department of Experimental and Clinical Medicine, University of Florence, Florence, Behçet Centre, Careggi University Hospital, Florence, Italy, and Centre for Inflammatory Diseases, Monash University Department of Medicine, Monash Medical Centre, Clayton, Victoria, Australia; <sup>5</sup>O. Karadag, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Vasculitis Research Center, Hacettepe University School of Medicine, Ankara, Turkey; <sup>6</sup>G. Espinosa, MD, PhD, Department of Autoimmune Diseases, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain; <sup>7</sup>M. Leclercq, MD, Internal Medicine Department, CHU Rouen, Rouen, France; <sup>8</sup>G. Simonini, MD, Rheumatology Unit, NEUROFARBA Department, Meyer Children's Hospital, University of Florence, Florence, Italy.

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Address correspondence to Dr. D. Saadoun, Hôpital Pitié-Salpêtrière, 83 Boulevard de l'hôpital, 75013 Paris, France. Email: david.saadoun@aphp.fr.

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Behçet disease (BD) is a systemic vasculitis of unknown origin affecting vessels of variable size.<sup>1,2</sup> Its classical clinical manifestations include recurrent oral and genital ulcers, pseudofolliculitis, erythema nodosum, and uveitis, and in the more severe forms, gastrointestinal, articular, vascular, and neurological manifestations.<sup>3,4</sup> Even if clinical manifestations are variable, different major clusters of the disease have been described: mucocutaneous and articular, extraparenchymal neurological and peripheral vascular, and parenchymal neurological and ocular.<sup>5</sup> Treatments for BD range from colchicine, low-dose glucocorticoids (GCs), topical GCs, and nonsteroidal antiinflammatory drugs for mucocutaneous and articular involvement to immunosuppressive therapies for ocular, vascular, neurological, and gastrointestinal symptoms. Prompt initiation of immunosuppressants such as GCs, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), interferon- $\alpha$ , cyclophosphamide (CYC), and biologic disease-modifying antirheumatic drugs (bDMARDs), in particular anti-tumor necrosis factor (anti-TNF) agents,<sup>6-8</sup> is mandatory in cases of life-threatening manifestations.<sup>9</sup>

Anti-TNF agents have proven effective in treating most BD clinical manifestations and their use is recommended as first-line therapy in patients with severe ocular, vascular, gastrointestinal, and central nervous system involvement.<sup>7,8</sup> Despite their efficacy, there is still a need for alternative therapies, as up to 35% of patients are refractory, intolerant, or present with

contraindications to anti-TNF agents.<sup>10</sup> Therefore, unmet therapeutic needs in BD have drawn attention to biologic agents targeting cytokines other than TNF.<sup>10-12</sup> Interleukin (IL)-6 seems to play an instrumental role in BD. High levels of IL-6 were found in sera of patients with BD, correlating with disease activity and arthritic manifestations.<sup>13</sup> In addition, high levels of IL-6 have also been detected in the cerebrospinal fluid of patients with neuro-BD and in the vitreal fluid of patients affected by autoimmune uveitis, contributing to ocular inflammation.<sup>14,15</sup> IL-6 stimulates the differentiation of T lymphocytes to Th17 lymphocytes, which act as proinflammatory mediators, with a concomitant reduction in regulatory T cells.<sup>16</sup> Tocilizumab (TCZ), a humanized antibody targeting the membrane IL-6 receptor, has been used thus far as an off-label therapy in a case series of patients with BD not responding to the approved treatments.<sup>17-23</sup> To date, the TCZ experience is limited in BD, and even if TCZ seems effective in most ophthalmological, neurological, vascular, and gastroenterological case series, conflicting results were obtained in terms of its effect on mucocutaneous and/or articular disease manifestations.

Herein, we aimed to evaluate TCZ efficacy in 3 different BD phenotypes (mucocutaneous and/or articular disease, ophthalmological, and neurological BD) in a multicenter cohort of 30 patients with refractory BD.

## METHODS

**Patients.** We conducted a multicenter retrospective study in referral hospitals from France, Italy, Spain, and Turkey between December 2021 and June 2022. All 30 enrolled patients met the criteria of the international study group for BD.<sup>24</sup> All patients had either mucocutaneous and/or articular manifestations, and/or uveitis, and/or neurological BD manifestations that were refractory to colchicine, csDMARDs, and/or bDMARDs. The study was performed according to the Declaration of Helsinki. According to our national policy, patients systematically received information on the electronic storage of their data for administrative and research purposes. They can exercise their right of opposition. No institutional review board approval is necessary.

**TCZ regimen.** TCZ was administered intravenously (IV) at 8 mg/kg every 4 weeks in 77% of patients or subcutaneously 162 mg once weekly in 23% of patients. Concomitant therapy included a stable dose of GC in 27 (90%) patients, colchicine in 12 (of 27, 44%), and csDMARDs in 7 (of 27, 26%).

**Data collection.** Demographic features and past medical history of BD were recorded. Data regarding BD manifestations, including oral and genital ulcers, skin manifestations, ophthalmological, vascular, and neurological involvement, were collected. Joint involvement was assessed using tender and swollen joint count. TCZ indication and route of administration, concomitant treatments, and previous failed therapies were also of special interest. Clinical variables, safety assessment, daily GC use, and laboratory findings were collected before TCZ therapy, at the time of TCZ first administration, after 3 months, 6 months (M6), and at the date of the last follow-up visit.

**End points.** The primary efficacy end point was the proportion of patients reaching a clinical response (complete or partial) at M6. Complete response (CR) was considered as the remission of the affected organs involved at baseline. Response to treatment was evaluated for each organ representing the indication for TCZ treatment and assessed as CR, partial response (PR), or nonresponse (NR). For the uveitis group, CR was defined as a complete resolution of uveitic macular edema (ME; central foveal thickness  $\leq$  300 mm with resolution of intraretinal cystic spaces) with a GC daily dosage of  $\leq$  10 mg at M6, without intraocular inflammation (grade 0 for anterior

chamber cells and vitreous haze).<sup>25</sup> PR was defined as an improvement of ME without complete resolution, an improvement of intraocular inflammation, and a reduction of the initial GC dosage at M6. Patients showing CR of uveitic ME with a GC dosage  $>$  10 mg/day at M6 were also considered to be partial responders. The remaining patients were considered nonresponders. For neurological BD, CR was defined as a complete clinical remission and imaging normalization (evaluated by magnetic resonance imaging) in the absence of neurological sequelae (defined as a Rankin score  $\leq$  1) at M6. PR was defined as an improvement, without imaging normalization. The remaining patients were considered to be nonresponders. For mucocutaneous and/or articular disease, CR was defined as the absence of oral and genital aphthae, skin lesions, and swollen joints at M6. PR consisted of the reduction of  $\geq$  50% in the number of oral and genital aphthae, skin lesions, and swollen joints at M6. The remaining patients were considered to be nonresponders.

Secondary end points included the proportion of patients with a CR, PR, and NR at M6; the disease relapse rate in the course of treatment; the TCZ steroid-sparing effect between baseline and M6; the TCZ retention rate; and the safety profile of TCZ.

**Statistical analysis.** Data are presented as a mean (SD) or median (IQR) for continuous variables, and as a percentage for qualitative variables. Wilcoxon signed-rank test was used to compare continuous variables and Fisher exact test to compare categorical variables. *P* values  $<$  0.05 were considered significant. Statistical analyses were performed using GraphPad Prism 6.0 (Dotmatics Inc.).

## RESULTS

**Characteristics of patients with BD.** We included 30 patients (17 women) with a median age at BD diagnosis of 30 (IQR 24-33) years. Baseline characteristics and outcomes are summarized in Tables 1, 2, 3, and 4.

Indications for TCZ were refractory uveitis in 18 (60%) patients, mucocutaneous and/or articular in 7 (23%), and neurological manifestations in 5 (17%; Table 2). One of the 7 patients with mucocutaneous and/or articular disease also presented with renal AA amyloidosis. HLA-B51 was positive in 14/19 (74%) subjects tested (Table 1).

Before TCZ, all patients had already received colchicine and 27 (90%) GCs. Patients received a median of 3 (IQR 2-4) courses of csDMARDs (azathioprine [48%], methotrexate [30%], CYC [30%], cyclosporine [19%], mycophenolate mofetil [7%], and tacrolimus [4%]) before TCZ treatment. Twenty-seven (90%) patients also received anti-TNF agents (11 [37%] and 3 [10%] patients received 2 or 3 anti-TNF agents, respectively), 5 (17%) anakinra, 2 (7%) ustekinumab, and 1 (3%) canakinumab prior to TCZ (Table 1).

**Efficacy.** TCZ was effective in 25 (83%) patients with BD at M6. Eighteen (60%) patients reached a CR, 7 (23%) PR, and 5 (17%) NR (Table 2).

Among the 18 patients treated for uveitis, TCZ was effective in 15 (83%) with a CR and PR in 12 (67%) and 3 (17%) patients, respectively (Table 3). Among the 3 nonresponders, 2 patients discontinued TCZ at month 2 and month 4, respectively, because of refractory retinal vasculitis. TCZ was effective for uveitic ME in 88% (CR 75%, PR 13%) and retinal vasculitis in 84% of patients (CR 67%, PR 17%). The mean visual acuity increased from 5.5 and 4.8 out of 10 (left and right eye, respectively) at baseline to 8.3 and 7.8, respectively, at M6.

Table 1. Demographic and clinical features of patients with BD.

	Value, n = 30
Female	17 (57)
Age at diagnosis, yrs, median (IQR)	30 (24-33)
HLA-B51 positivity	14 (74)
Clinical manifestations	
Oral ulcers	28 (93)
Genital ulcers	16 (53)
Skin lesions	22 (73)
Uveitis	21 (70)
Retinal vasculitis	14 (47)
Macular edema	9 (30)
Arthralgia	19 (63)
Venous thrombosis	5 (17)
Arterial aneurysm	1 (3)
Neurological	5 (17)
Gastrointestinal	6 (20)
Treatments before TCZ	
No. of lines of treatment, median (IQR)	3 (2-4)
Conventional immunosuppressants	
Azathioprine	13 (48)
Methotrexate	8 (30)
Cyclophosphamide	8 (30)
Interferon- $\alpha$	8 (30)
Cyclosporine	5 (19)
Mycophenolate mofetil	2 (7)
Tacrolimus	1 (4)
Biologic agents	
Adalimumab	18 (67)
Infliximab	17 (63)
Anakinra	5/27 (19)
Golimumab	3 (11)
Etanercept	2 (7)
Ustekinumab	2 (7)
Certolizumab pegol	1/27 (4)
Canakinumab	1/27 (4)

Values are n (%) unless otherwise indicated. BD: Behçet disease; TCZ: tocilizumab.

TCZ was effective in all patients with neurological manifestations (CR 60%, PR 40%; Table 4).

Among the 7 patients treated for mucocutaneous and/or articular disease, a clinical response was obtained in 5 (71%) patients (CR 42%, PR 29%; Table 4). Two patients presenting with pyoderma gangrenosum as a cutaneous manifestation had a CR, as well as a patient with renal AA amyloidosis (Table 4).

TCZ demonstrated a GC-sparing effect. The median daily prednisone dose dropped from 20 (IQR 10-40) mg/day to 9 (IQR 5-13) mg at M6 ( $P < 0.001$ ) and 5 (IQR 0-9) mg at the last visit of follow-up. Three of the 7 patients receiving concomitant csDMARDs were able to withdraw these therapies at M6.

**TCZ retention rate.** After a median follow-up of 31 (IQR 21-56) months, 13 (43%) patients were still receiving TCZ and maintained remission. The 17 (57%) remaining patients discontinued TCZ as a result of side effects, failure, and/or relapse ( $n = 12$ ) or after achieving remission ( $n = 5$ ; Tables 2, 3, and 4).

Table 2. Efficacy and safety of TCZ in patients with BD.

	Value
BD duration, mos, median (IQR)	106 (32-172)
Indication for TCZ	
Uveitis	18 (60)
Neurological	5 (17)
Mucocutaneous and/or articular	7 (23)
TCZ treatment	
Intravenous	23 (77)
Subcutaneous	7 (23)
Combined GCs	27 (90)
Daily dose of GCs, mg, median (IQR)	20 (10-40)
Combined immunosuppressants	7 (26)
TCZ treatment duration, mos, median (IQR)	21 (8-38)
Follow-up duration, mos, median (IQR)	31 (21-56)
Overall response	
Complete response	18 (60)
Partial response	7 (23)
Nonresponse	5 (17)
Relapse	2 (8)
Safety	n, (%)
Any AEs	9 (30)
Serious AEs	3 (10)
Pneumonia	1 (3)
Digestive perforation	1 (3)
Sepsis	1 (3)

Values are n (%) unless otherwise indicated. AE: adverse event; BD: Behçet disease; GC: glucocorticoid; TCZ: tocilizumab.

**Safety.** Under TCZ therapy, mild to moderate side effects were observed in 6 (20%) patients and included skin rash ( $n = 2$ ), worsening of mucocutaneous disease manifestations ( $n = 1$ ), recurrent urinary tract infections ( $n = 1$ ), neutropenia ( $n = 1$ ), and dyslipidemia ( $n = 1$ ). Three (10%) patients presented serious adverse events (pneumonia, intestinal perforation, and septicemia) requiring therapy discontinuation in 2 cases (Table 2).

## DISCUSSION

Despite the efficacy of anti-TNF agents, there is still a need for alternative therapies, as up to 35% of patients are refractory, intolerant, or present contraindications to these agents.<sup>10</sup> Therefore, unmet therapeutic needs in BD have drawn attention to biologic agents targeting cytokines other than TNF.<sup>10</sup> IL-6 seems to play a pivotal role in BD, and TCZ represents a possible new therapeutic strategy.<sup>11</sup> Currently, the TCZ experience is limited in BD, and even if TCZ seems effective in case series, conflicting results were obtained in terms of its effect on mucocutaneous and/or articular disease manifestations.

Herein, we report the largest experience of TCZ that we know of in patients with refractory BD. Ninety percent of our patients with BD were refractory or intolerant to anti-TNF agents. TCZ was administered IV in most of our patients. We could evaluate TCZ efficacy in 3 main BD phenotypes such as uveitis, neurological, and mucocutaneous and articular manifestations. The main conclusions drawn by this study are: (1) TCZ seems to be an effective alternative to anti-TNF agents in patients with

Table 3. Outcomes of patients with BD treated with TCZ for uveitis.

Patient No.	Sex/ Age <sup>a</sup>	Prior Immunosuppressive Drug	Associated Immunosuppressive Drug	Main Symptoms	Other Symptoms	Response at M6	Corticosteroids at Baseline/M6, mg	Relapse	Side Effects
1	F/33	ADA, IFX, MTX	-	Uveitis, RV	Oral ulcers, genital ulcers, erythema nodosum, arthralgia, GI involvement	CR	0/0	-	-
2	F/16	ADA, GOL	-	Uveitis, RV	Oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum, arthralgia	CR	20/0	-	-
3	F/29	AZA, ADA, MTX, IFX	MTX	Uveitis, ME	Oral ulcers, carotid arterial aneurysm	CR	20/9	-	-
4	F/65	IFN- $\alpha$ , ADA	-	Uveitis, ME	Oral ulcers, arthralgia	CR	15/5	-	Neutropenia
5	F/24	AZA, IFN- $\alpha$ , ANK, IFX	-	Uveitis, RV, ME	Oral ulcers, arthralgia	CR	15/10	-	-
6	M/21	IFN- $\alpha$	-	Uveitis, RV, ME	Oral ulcers, pyoderma gangrenosum	PR	35/NA	-	Skin rash
7	F/26	AZA, ADA	-	Uveitis, RV	Oral ulcers, genital ulcers, pseudofolliculitis, hidradenitis suppurativa, arthralgias	CR	15/5	-	-
8	M/9	ADA, MTX	-	Uveitis	Oral ulcers	PR	5/0	-	-
9	M/27	CYC, IFX, ADA, GOL	-	Uveitis, RV, ME	Arthralgias	CR	20/15	Yes	-
10	M/24	IFX, ADA, AZA	-	Uveitis, RV	Oral ulcers, genital ulcers, arthralgias	PR	10/10	Yes	-
11	M/29	CYC, IFN- $\alpha$ , IFX, MME, ADA, ANK, MTX	-	Uveitis, RV	Oral ulcers, pseudofolliculitis	NR	40/NA	-	-
12	F/32	AZA, CYC, IFN- $\alpha$ , ANK, IFX	-	Uveitis, ME	Oral ulcers, genital ulcers, pseudofolliculitis, arthralgia, venous thrombosis, pericarditis	CR	10/9	-	Recurrent UTI
13	M/31	Yes, but NA	NA	Uveitis, RV	Oral ulcers	CR	40/15	-	-
14	M/32	Yes, but NA	NA	Uveitis, RV	Oral ulcers, pseudofolliculitis, arthralgias	CR	80/16	-	-
15	M/29	Yes, but NA	NA	Uveitis, RV	Oral ulcers, pseudofolliculitis	NR	70/NA	-	-
16	M/22	AZA, IFX, ADA, CYC	Yes, but NA	Uveitis, ME	Oral ulcers, papulopustular lesions, erythema nodosum	NR	64/48	-	-
17	F/48	IFX, ADA	-	Uveitis, ME	Oral ulcers, genital ulcers, pseudofolliculitis, arthralgia	CR	20/9	-	Dyslipidemia
18	M/32	ADA	-	Uveitis, RV	Oral ulcers, pseudofolliculitis, arthralgias	CR	80/8	-	-

<sup>a</sup>Age is in years. ADA: adalimumab; ANK: anakinra; AZA: azathioprine; BD: Behçet disease; CR: complete response; CYC: cyclophosphamide; F: female; GI: gastrointestinal; GOL: golimumab; IFN- $\alpha$ : interferon- $\alpha$ ; IFX: infliximab; M: male; M6: 6 months after TCZ initiation; ME: macular edema; MME: mycophenolate mofetil; MTX: methotrexate; NA: not available; NR: nonresponse; PR: partial response; RV: retinal vasculitis; TCZ: tocilizumab; UTI: urinary tract infections.

BD with refractory uveitis and neurological manifestations, and (2) the efficacy of TCZ seems less clear in the mucocutaneous and articular phenotype.

In a systematic literature review, Akiyama et al analyzed the outcomes of TCZ in 47 patients with refractory BD, concluding that anti-IL-6 treatment could be a valid alternative for refractory ocular, neurological, and vascular BD, as well as for secondary AA amyloidosis, but not for mucocutaneous and articular forms.<sup>26</sup> Previous case reports have indeed highlighted the diversity of response rates to TCZ among the different disease clusters, confirming good efficacy in ophthalmological, neurological, and vascular disease with conflicting results for the articular and mucocutaneous phenotype<sup>15-21,25-29</sup> (Table 5).

In our series, ophthalmological manifestations were well-controlled by TCZ, with a recovery in 84% of patients and a beneficial effect on uveitic ME in 88% of cases and on retinal vasculitis in 84% of subjects. This is in agreement with previous studies of TCZ in BD uveitis<sup>21,27</sup> (Table 5). Atienza-Mateo et al highlighted the efficacy of TCZ (CR 63%, PR 19%) in 16 patients with BD uveitis who did not respond to conventional

and anti-TNF agents (Table 5). Eser Ozturk et al reported 5 patients with sight-threatening BD uveitis who were refractory to interferon- $\alpha$  and conventional and anti-TNF agents; all cases achieved CR with TCZ treatment (Table 5). Leclercq et al compared TCZ and anti-TNF agents in refractory uveitic ME, showing TCZ superiority.<sup>28</sup> Many other single case reports or limited case series showed the efficacy of TCZ in ocular BD manifestations.<sup>18,19,29,30</sup>

For neurological involvement, TCZ was also able to induce remission in all our patients. These results are consistent with previous reports. Liu et al treated 11 patients with BD with refractory neurological involvement achieving a CR in 20% and PR in 80% of cases<sup>31</sup> (Table 5). Atienza-Mateo et al reported efficacy of TCZ in 5 patients with refractory neurological BD (3 CR and 1 stabilization<sup>21</sup>; Table 5). Many other single case reports or limited case series confirm this trend.<sup>17,32-34</sup>

We could not evaluate the efficacy of TCZ in vascular BD because none of our patients were treated for vascular involvement. TCZ showed good results in vascular BD in a previous Chinese study, in which 9 of the 10 patients with vascular BD

Table 4. Outcomes of patients with BD treated with TCZ for neurological or mucocutaneous and/or articular manifestations.

Patient	Sex/ Age <sup>a</sup>	Prior Immunosuppressive Drug	Associated Immunosuppressive Drug	Main Symptoms	Other Symptoms	Response at M6	Corticosteroids at Baseline/M6, mg	Relapse	Side Effects
1	F/33	AZA, IFX, ADA	-	Neurological BD (meningitidis, parenchymal lesions, myelitis, MRI alterations)	Uveitis, oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum, arthralgias	CR	0/0	-	-
2	F/24	CsA, MTX, AZA, TAC, IFN- $\alpha$ , CYC, IFX, ADA, CZP, ANK	Yes, but NA	Neurological BD (optic neuropathy)	Oral ulcers, genital ulcers, arthralgias, GI involvement	PR	38/14	-	-
3	F/32	CsA, IFX, AZA	-	Neurological BD (meningitidis, parenchymal lesions, MRI)	Oral ulcers, genital ulcers, papulopustular abdominal lesions	CR	50/5	-	-
4	M/33	MTX, CYC, MMF, AZA	-	Neurological BD (parenchymal lesions, myelitis, MRI alterations), arthralgias and arthritis	Uveitis, RV, venous thrombosis	CR	5/5	-	Pneumonia
5	F/48	AZA, CYC, IFX, IFN- $\alpha$ , chlorambucil	MTX then MMF	Neurological BD (parenchymal lesions, optic neuropathy, MRI alterations)	Oral ulcers, genital ulcers, erythema nodosum, papulopustular lesions, leucocytoclastic vasculitis, livedo reticularis, venous thrombosis, GI involvement	PR	50/25	-	Sepsis (TCZ stopped at M30)
6	F/24	MTX, IFX, ADA	-	Oral ulcers, genital ulcers, arthralgias and arthritis	Uveitis, RV, ME	PR	23/15	-	Sepsis with digestive perforation (TCZ stopped at M9)
7	F/34	GOL, ADA	-	Oral ulcers, genital ulcers, pseudofolliculitis, arthralgias and arthritis	Venous thrombosis, GI involvement	PR	10/8	-	-
8	F/20	AZA, IFX, UST	UST	Oral ulcers, genital ulcers, pseudofolliculitis, pyoderma gangrenosum	GI involvement	CR	20/8	-	-
9	F/36	CsA, IFX, ANK, CYC, UST	UST	Oral ulcers, pyoderma gangrenosum, arthralgias	-	CR	10/0	-	-
10	M/27	AZA, MTX, IFX, ADA, ETN, CYC, CsA, CNK, IFN- $\alpha$	-	Oral ulcers, genital ulcers, pseudofolliculitis, arthralgias	-	NR	3/0	-	Worsening of mucocutaneous manifestations (TCZ stopped at M2)
11	F/43	MTX, ADA, ETN	Yes, but NA	Oral ulcers, genital ulcers, erythema nodosum, arthralgias and arthritis	GI involvement, myocarditis	NR	25/NA	-	Skin rash (TCZ stopped at M3)
12	M/40	-	-	Renal AA amyloidosis	Oral ulcers, genital ulcers, papulopustular lesions, arthralgias	CR	0/0	-	-

<sup>a</sup> Age is in years. ADA: adalimumab; ANK: anakinra; AZA: azathioprine; BD: Behçet disease; CNK: canakinumab; CR: complete response; CsA: cyclosporine; CYC: cyclophosphamide; CZP: certolizumab pegol; ETN: etanercept; F: female; GI: gastrointestinal; GOL: golimumab; IFN- $\alpha$ : interferon- $\alpha$ ; IFX: infliximab; M: male; M2, 3, 6, 9, 30: 2, 3, 6, 9, or 30 months after TCZ initiation; ME: macular edema; MMF: mycophenolate mofetil; MRI: magnetic resonance imaging; MTX: methotrexate; NA: not available; NR: nonresponse; PR: partial response; RV: retinal vasculitis; TAC: tacrolimus; TCZ: tocilizumab; UST: ustekinumab.

obtained a clinical response (CR 50%, PR 40%<sup>35</sup>; Table 5). Ding et al reported a cohort of 7 patients with vascular BD refractory to GCs and csDMARDs, achieving a clinical response with TCZ (CR 42%, PR 42%, and 1 patient nonevaluable because of premature discontinuation due to financial issues<sup>20</sup>; Table 5).

Reports on the effects of TCZ on mucocutaneous and articular lesions are contradictory.<sup>13-15,17-19,30-32</sup> Among our mucocutaneous and articular cluster, we obtained a lower remission rate as compared to other clinical phenotypes. In the literature, TCZ had few effects on oral ulcerations in some case series.<sup>21,22,36</sup> Worsening of mucocutaneous lesions after TCZ has also been

reported, sometimes requiring drug discontinuation.<sup>17,23,37</sup> IL-6, in fact, is an important key factor in wound healing, so its reduction may impair the cutaneous and mucosal healing process.<sup>38</sup>

For joint manifestations of BD, literature results on TCZ are also conflicting. In the case series by Atienza-Mateo et al, 4 of 7 patients improved, with a CR in 2 cases.<sup>21</sup> In contrast, many other reports pointed out the failure of TCZ for articular symptoms.<sup>19,23</sup> In line with these previous experiences, our data show poor efficacy of TCZ on joint manifestations in BD. One patient in our study with mucocutaneous and articular disease, and who

Table 5. Case series of patients with BD treated with TCZ.

Reference	n	Clinical Manifestations	Previous Treatments	TCZ Indication	Route of TCZ Administration (IV or SC)	TCZ-Associated Treatments	Clinical Outcomes (%)	Prednisone Daily Dose, Baseline to M6, mg	SAEs	Median Follow-Up Under TCZ, mos, median (IQR)	Relapse, n (mos of TCZ therapy)
Zhong <sup>35</sup>	10	Vascular disease (10), arterial (10), venous (2), mucocutaneous (10), GI (1), uveitis (1), joints (2)	GCs (10), CYC (7), MMF (2), AZA (2), TAC (1)	Vascular disease (10)	IV (10)	GCs (9)	Vascular: CR (50), PR (40), NR (10) Cutaneous: CR (100)	55 to 8	None	27 (7-35) <sup>a</sup>	1 (7)
Ding <sup>20</sup>	7	Vascular disease (7), arterial (7), venous (2)	GCs (7), CYC (7), AZA (5), MTX (2), TAC (1), ETN (1), LEF (2)	Vascular disease (7)	IV (7)	GCs (7), AZA (5), CYC (4), LEF (1), MTX (1)	Vascular: CR (43), PR (43) <sup>b</sup>	27 ± 17 to 9 ± 3	None	19 (4-33) <sup>a</sup>	None
Atienza-Mateo <sup>21</sup>	16	Uveitis (16), mucocutaneous (10), neurological (5), joints (7), venous (1), and GI (1)	MTX (13), CsA (8), AZA (6), CYC (3), MMF (1), ADA (10), IFX (7), GOL (3), CNK (1), CZP (1), ETN (1), COL (3), THD (1)	Uveitis (14); CME (9), RV (5) and neurological BD (2)	IV (13), SC (3)	MTX (3), AZA (3), MMF (1), and CsA (1)	Ocular: CR (63), PR (19), NR (19) Neurological BD: CR (60), PR (20) <sup>b</sup> Joints: CR (29), PR (29), NR (43)	NA	Severe infusion reaction (1), cellulitis with sepsis (1)	20 (9-45)	None
Liu <sup>31</sup>	11	Neurological (11), mucocutaneous (11), uveitis (3), joints (2), vascular (2)	GCs (11), CYC (8), AZA (6), MTX (5), CsA (2), TAC (1), MMF (1), intrathecal injection of dexamethasone and MTX (5), IFX (5), IFN-α (3), daclizumab (1)	Neurological BD (11)	IV (11)	GCs (11), MTX (3), CYC (3), AZA (2)	Neurological: CR (18), PR (82)	69 ± 17 to 16 ± 16	None	13 (3-23)	2 (8; 18)
Eser Oztruk <sup>27,5</sup>	5	Uveitis (5) and vascular disease (1)	GCs (5), AZA (5), CsA (4), IFN-α (5), IFX (5), ADA (2), MMF (1), PSTA injections (2), IV dexamethasone injection (4), bevacizumab ocular injection (1)	Uveitis (5); CME (4), RV (3)	IV (5)	Oral GCs (3), AZA (2), CsA (1), IV dexamethasone injection (1)	Uveitis: CR (100); CME: CR (75), PR (25); RV: CR (100)	NA	None	11 (5-19)	None

Reference	n	Clinical Manifestations	Previous Treatments	TCZ Indication	Route of TCZ Administration (IV or SC)	TCZ-Associated Treatments	Clinical Outcomes (%)	Prednisone Daily Dose, Baseline to M6, mg	SAEs	Median Follow-Up Under TCZ, mos, median (IQR)	Relapse, n (mos of TCZ therapy)
Khritri	30	Oral ulcers (28), genital ulcers (16), skin lesions (22), uveitis (21), joints (19), vascular disease (6), neuro-BD (5), GI involvement (6), AA amyloidosis (1)	GCs (28), ADA (18), IFX (17), AZA (13), MTX (8), GOL (3), IFN- $\alpha$ (8), ANK (5), CYC (8), CsA (5), TAC (1), CZP (1), UST (2), ETN (2), CNK (1), MMF (2)	Uveitis (18), neurological BD (5), mucocutaneous and/or articular (7)	IV (23), SC (7)	GCs (28), DMARDs (7)	Overall: CR + PR (83), CR (60), PR (23), NR (17) Uveitis: CR + PR (83), CR (67), PR (17) Neurological: CR + PR (100), CR (60), PR (40) Mucocutaneous and/or articular: CR + PR (71), CR (42), PR (29)	20 to 9	Pneumonia (1), Sepsis (1) infection with digestive perforation (1)	21 (8-38)	2

Values are number of patients unless otherwise indicated. <sup>a</sup> Median follow-up in months (TCZ therapy and posttherapy follow-up). <sup>b</sup> One patient was not evaluable because of premature drug discontinuation. ADA: adalimumab; ANK: anakinra; AZA: azathioprine; BD: Behçet disease; CME: cystoid macular edema; CNK: canakinumab; COL: colchicine; CR: complete response; CsA: cyclosporine; CYC: cyclophosphamide; CZP: certolizumab pegol; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; GC: glucocorticoid; GI: gastrointestinal; GOL: golimumab; IFN- $\alpha$ : interferon- $\alpha$ ; IFX: infliximab; IV: intravenous; LEF: leflunomide; M6: 6 months after TCZ initiation; MMF: mycophenolate mofetil; MTX: methotrexate; NA: not available; NR: nonresponse; PR: partial response; PSTA: posterior subtenon triamcinolone acetate; RV: retinal vasculitis; SAE: severe adverse event; SC: subcutaneous; TAC: tacrolimus; TCZ: tocilizumab; THD: thalidomide; UST: ustekinumab.

also presented with renal AA amyloidosis, obtained a CR with TCZ. Two cases of BD-related secondary renal AA amyloidosis treated with TCZ have been reported in the literature, and in both cases a CR was obtained.<sup>39,40</sup> Finally, TCZ was effective in sparing GCs in our series and in published case reports<sup>20,31,35</sup> (Table 5).

We do not report new safety signals of TCZ. Common side effects of TCZ such as neutropenia, thrombocytopenia, dyslipidemia, increased transaminase level, and upper respiratory tract infections were observed in 30% of our patients with BD, in line with previous reports.<sup>41</sup> We observed 2 cases of severe sepsis requiring treatment interruption, including a patient presenting with an intestinal perforation—a well-known drug-related side effect.<sup>42,43</sup>

This study presents some limitations. Its retrospective nature could not allow for the evaluation of the exact number of oral and genital ulcers every month, as well as the exact number of swollen joints. Another limitation is the small number of subjects affected by neurological and mucocutaneous/articular disease forms.

In conclusion, our study provides the results of the largest cohort of patients, that we know of, with refractory BD treated with TCZ. Ninety percent of patients with BD were refractory or intolerant to anti-TNF agents. We highlight that TCZ seems to be an effective alternative to anti-TNF agents in patients with BD with refractory uveitis and neurological manifestations. Further prospective studies are warranted to confirm these results.

## REFERENCES

- Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med* 1999;341:1284-91.
- Davatchi F, Chams-Davatchi C, Shams H, et al. Behçet's disease: epidemiology, clinical manifestations, and diagnosis. *Expert Rev Clin Immunol* 2017;13:57-65.
- Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990;335:1078-80.
- Bettiol A, Prisco D, Emmi G. Behçet: the syndrome. *Rheumatol* 2020;59 Suppl 3:iii101-7.
- Seyahi E. Phenotypes in Behçet's syndrome. *Intern Emerg Med* 2019;14:677-89.
- Alibaz-Oner F, Direskeneli H. Advances in the treatment of Behçet's disease. *Curr Rheumatol Rep* 2021;23:47.
- Haremi 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.
- Arida A, Fragiadaki K, Giavri E, Sfikakis PP. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. *Semin Arthritis Rheum* 2011;41:61-70.
- Alpsoy E, Leccese P, Emmi G, Ohno S. Treatment of Behçet's disease: an algorithmic multidisciplinary approach. *Front Med* 2021;8:624795.
- Arida A, Sfikakis PP. Anti-cytokine biologic treatment beyond anti-TNF in Behçet's disease. *Clin Exp Rheumatol* 2014;32 Suppl 84:S149-55.
- Mirouse A, Barette S, Desbois AC, et al. Long-term outcome of ustekinumab therapy for Behçet's disease. *Arthritis Rheumatol* 2019;71:1727-32.
- Fagni F, Bettiol A, Talarico R, et al. Long-term effectiveness and safety of secukinumab for treatment of refractory mucosal and

- articular Behçet's phenotype: a multicentre study. *Ann Rheum Dis* 2020;79:1098-104.
13. Talaat RM, Sibaii H, Bassyouni IH, El-Wakkad A. IL-17, IL-10, IL-6, and IFN- $\gamma$  in Egyptian Behçet's disease: correlation with clinical manifestations. *Eur Cytokine Netw* 2019;30:15-22.
  14. Hirohata S, Isshi K, Oguchi H, et al. Cerebrospinal fluid interleukin-6 in progressive neuro-Behçet's syndrome. *Clin Immunol Immunopathol* 1997;82:12-7.
  15. Yoshimura T, Sonoda KH, Ohguro N, et al. Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis. *Rheumatol* 2009;48:347-54.
  16. Liang L, Wang H, Peng XY, Zhao M. [The changes of Th lymphocyte subsets in patients with Behcet disease]. [Article in Chinese] *Zhonghua yan ke za zhi* 2011;47:393-7.
  17. Shapiro LS, Farrell J, Borhani Haghighi A. Tocilizumab treatment for neuro-Behçet's disease, the first report. *Clin Neurol Neurosurg* 2012;114:297-8.
  18. Hirano T, Ohguro N, Hohki S, et al. A case of Behçet's disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Mod Rheumatol* 2012;22:298-302.
  19. Deroux A, Chiquet C, Bouillet L. Tocilizumab in severe and refractory Behçet's disease: four cases and literature review. *Semin Arthritis Rheum* 2016;45:733-7.
  20. 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. *Rheumatol* 2018;57:2057-9.
  21. Aienza-Mateo B, Beltrán E, Hernández-Garfella M, et al. Tocilizumab in Behçet's disease with refractory ocular and/or neurological involvement: response according to different clinical phenotypes. *Clin Exp Rheumatol* 2021;39 Suppl 132:37-42.
  22. Terreaux W, Mestrallet S, Fauconier M, et al. Failure of tocilizumab therapy in a patient with mouth and genital ulcers with inflamed cartilage syndrome complicated by aortic aneurysm. *Rheumatol* 2015;54:2111-3.
  23. Emmi G, Silvestri E, Squatrito D, Emmi L, Cantarini L, Prisco D. Tocilizumab-induced exacerbation of mucosal ulcers in a patient with multi-refractory Behçet's disease. *Semin Arthritis Rheum* 2016;46:e1-2.
  24. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014;28:338-47.
  25. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* 1985;92:467-71.
  26. Akiyama M, Kaneko Y, Takeuchi T. Effectiveness of tocilizumab in Behçet's disease: a systematic literature review. *Semin Arthritis Rheum* 2020;50:797-804.
  27. Eser Ozturk H, Oray M, Tugal-Tutkun I. Tocilizumab for the treatment of Behçet uveitis that failed interferon alpha and anti-tumor necrosis factor-alpha therapy. *Ocul Immunol Inflamm* 2018;26:1005-14.
  28. Leclercq M, Andrillon A, Maalouf G, et al. Anti-tumor necrosis factor  $\alpha$  versus tocilizumab in the treatment of refractory uveitic macular edema: A multicenter study from the French uveitis network. *Ophthalmology* 2022;129:520-9.
  29. Alokaily F, Al Saati A, Jawad A. Successful treatment of Behçet's uveitis with tocilizumab. *Saudi J Ophthalmol* 2017;31:42-4.
  30. 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.
  31. Liu J, Yan D, Wang Z, et al. Tocilizumab in the treatment of severe and refractory parenchymal neuro-Behçet's syndrome: case series and literature review. *Ther Adv Musculoskelet Dis* 2020;12:1759720X20971908.
  32. Urbaniak P, Hasler P, Kretzschmar S. Refractory neuro-Behçet treated by tocilizumab: a case report. *Clin Exp Rheumatol* 2012;30 Suppl 72:S73-5.
  33. Addimanda O, Pipitone N, Pazzola G, Salvarani C. Tocilizumab for severe refractory neuro-Behçet: three cases IL-6 blockade in neuro-Behçet. *Semin Arthritis Rheum* 2015;44:472-5.
  34. Essaoudouni L, Ha-Ou-Nou FZ. Efficacy and safety of tocilizumab in neuro-Behçet's disease: a case report. *Rev Neurol* 2017;173:171-2.
  35. Zhong H, Liu T, Liu Y, Zhang X, Zhou Y, Su Y. Efficacy and safety of tocilizumab in Behçet's syndrome with refractory arterial lesions: a single-centre observational cohort study in China. *Rheumatol* 2022;61:2923-30.
  36. Diamantopoulos AP, Hatemi G. Lack of efficacy of tocilizumab in mucocutaneous Behçet's syndrome: report of two cases. *Rheumatol* 2013;52:1923-4.
  37. Cantarini L, Lopalco G, Vitale A, et al. Paradoxical mucocutaneous flare in a case of Behçet's disease treated with tocilizumab. *Clin Rheumatol* 2015;34:1141-3.
  38. Johnson BZ, Stevenson AW, Prêle CM, Fear MW, Wood FM. The role of IL-6 in skin fibrosis and cutaneous wound healing. *Biomedicine* 2020;8:101.
  39. Ilbay A, Erden A, Sari A, et al. Successful treatment of amyloid A-type amyloidosis due to Behçet disease with tocilizumab. *J Clin Rheumatol* 2019;25:43-5.
  40. Redondo-Pachón MD, Enríquez R, Sirvent AE, et al. Tocilizumab treatment for nephrotic syndrome due to amyloidosis in Behçet's disease. *Ren Fail* 2013;35:547-50.
  41. McLaughlin M, Östör A. Safety of subcutaneous versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. *Expert Opin Drug Saf* 2015;14:429-37.
  42. Curtis JR, Perez-Gutthann S, Suissa S, et al. Tocilizumab in rheumatoid arthritis: a case study of safety evaluations of a large postmarketing data set from multiple data sources. *Semin Arthritis Rheum* 2015;44:381-8.
  43. Gout T, Ostör AJK, Nisar MK. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. *Clin Rheumatol* 2011;30:1471-4.