

Tocilizumab in Behcet's disease

Tocilizumab in Behcet's disease: a multicentre study of 30 patients

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Abstract

Objective. To evaluate tocilizumab (TCZ) efficacy in refractory Behcet's Disease (BD) patients.

Methods. Multicenter study of 30 patients fulfilling the International Criteria for BD and treated with TCZ at different European referral centres. The clinical response was evaluated at 6 months (M6) from TCZ initiation.

Results. Ninety percent of BD patients were refractory or intolerant to anti-TNF- α agents. Overall, TCZ was effective in 25 (83%) BD patients of whom 18 (60%) and 7 (23%) were complete and partial responders, respectively. The complete response was of 67%, 60% and 42% in patients with uveitis (18/30), neurological (5/30) and muco-cutaneous and/or articular (7/30) manifestations, respectively. TCZ had a significant steroid-sparing effect allowing to decrease the median daily prednisone dose from 20mg/day [10-40] to 9mg [5-13] at 6 months ($p < 0.001$). The number of BD patients needing concomitant DMARDs 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 serious adverse events [pneumonia, intestinal perforation, and septicemia] requiring therapy discontinuation in 2 cases.

Conclusion. TCZ seems an effective alternative to anti-TNF- α agents in BD uveitis and neurological manifestations.

INTRODUCTION

Behcet's disease (BD) is a systemic vasculitis of unknown origin affecting vessels of variable size (1,2). Its classical clinical manifestations include recurrent oral and genital ulcers, pseudo folliculitis, erythema nodosum and uveitis, and in the more severe forms, gastrointestinal, articular, vascular and neurological manifestations (3,4). Even if clinical manifestations are variable, different major clusters of the disease have been described: the muco-cutaneous and articular, the extra-parenchymal neurological and peripheral vascular, the parenchymal neurological and ocular (5). Treatments of BD range from colchicine, low doses glucocorticoids (GC), topic GC and non-steroidal anti-inflammatory drugs (NSAIDs) for muco-cutaneous and articular involvements to immunosuppressive therapies for ocular, vascular, neurological and gastrointestinal symptoms. Prompt initiation of immunosuppressants such as GC, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), interferon- α , cyclophosphamide and biological disease-modifying antirheumatic drugs (bDMARDs), in particular anti tumor necrosis factor- α (TNF- α) agents (6–8) is mandatory in case of life-threatening manifestations (9).

Anti-TNF- α agents proved effective in treating most of BD clinical manifestations and their use is recommended as first-line therapy in patients with severe ocular, vascular, gastrointestinal and central nervous system (CNS) involvement (7,8). Despite their efficacy, there is still need for alternative therapies, as up to 35% of patients are refractory, intolerant or present contraindications to anti-TNF- α agents (10). Therefore, unmet therapeutic needs in BD have drawn recent attention to biological agents targeting cytokines other than TNF- α (10–12). IL-6 seems to play an instrumental role in BD. High levels of IL-6 were found in sera of BD patients, correlating with disease activity and arthritic manifestations (13). In addition, high levels of IL-6 have also been detected in the cerebro-spinal fluid of neuro-BD patients and in

vitreal fluid of patients affected by autoimmune uveitis, contributing to ocular inflammation (14,15). IL-6 stimulates the differentiation of T lymphocytes to T helper 17 (Th17) lymphocytes which act as pro-inflammatory mediators, with a concomitant reduction in regulatory T cells (Tregs) (16). Tocilizumab (TCZ), a humanized antibody targeting the membrane IL-6 receptor, has been used so far as off-label therapy in case series of BD patients non-responding to the approved treatments (17–23). To date the TCZ experience is limited in BD and even if it seems effective in most ophthalmological, neurological, vascular, and gastroenterological case-series, conflicting results were obtained in muco-cutaneous and/or articular disease manifestations.

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

MATERIAL AND METHODS

Patients

We conducted a multicentre retrospective study in referral hospitals from France, Italy, Spain and Turkey between December 2021 and June 2022. All the 30 enrolled patients met the criteria of the international study group for BD (24). All patients had either muco-cutaneous 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 IRB approval is necessary.

TCZ regimen

TCZ was administered intravenously at 8mg/kg every 4 weeks in 77% of patients or subcutaneously 162 mg once a week in 23%. Concomitant therapy included stable dose of GC in 27 (90%) patients, colchicine in 12 (41%) and csDMARDs in 7 (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 joints count. TCZ indication and way of administration, concomitant treatments and previous failed therapies were also of special interest. Clinical parameters, safety assessment, daily GC use and laboratory findings were collected before TCZ therapy, at the time of TCZ first administration (T0), after three months (M3), six months (M6) and at the date of the last follow-up visit.

Endpoints

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) and non-response (NR). For the uveitis group, CR was defined as a complete resolution of uveitic macular edema (ME) (central foveal thickness (CFT) \leq 300 μ m with resolution of intraretinal cystic spaces) with a GC daily dosage of 10 mg or less at M6, without intraocular inflammation (grade 0 for anterior chamber cells and vitreous haze) (25). 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 complete resolution of uveitic ME with a GC dosage greater than 10 mg/day at M6 were also considered to be partial responders. The remaining patients were considered non-responders. For neurological BD, CR was defined as a complete clinical remission, imaging (evaluated by magnetic resonance (MRI)) normalisation in the absence of neurological sequelae (defined as a Rankin score ≤ 1) at M6. PR was defined as an improvement, without imaging normalisation. The remaining patients were considered NR. For muco-cutaneous and/or articular disease, CR was defined as the absence of oral and genital aphthae, skin lesions and swollen joints at M6; PR consisted in 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 NR.

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

Statistical analysis

Data are presented as a mean (SD) or median [IQR] for continuous variables and as a percentage for qualitative variables. Wilcoxon's test was used to compare continuous variables and Fisher's exact test to compare categorical variables. P values less than 0.05 were considered significant. Statistical analyses were performed using GraphPad Prism 6.0.

RESULTS

Characteristics of BD patients

We included 30 patients (17 women) with a median age at BD diagnosis of 30 years (IQR 24–33 years).

Baseline characteristics and outcomes are summarized in **Table 1, 2, 3 and 4**.

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

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

Efficacy

TCZ was effective in 25 (83%) BD patients 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 complete and partial response in 12 (67%) and 3 (17%) patients, respectively (**Table 3**). Among the three NR, two patients

discontinued TCZ at M2 and M4, respectively due to refractory retinal vasculitis. TCZ was effective on uveitic macular edema in 88% (CR 75%, PR 13%) and on retinal vasculitis in 84% of patients (CR 67%, PR 17%). The mean visual acuity increased from 5.5/4.8 out of 10 (left/right eyes) at baseline to 8.3/7.8 at M6.

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

Among the 7 patients treated for muco-cutaneous and/or articular disease, a clinical response was obtained in 5 (71%) patients (CR 42%, PR 29%) (**Table 4**). Two patients presenting pyoderma gangrenosum as 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 20mg/day [10-40] to 9mg [5-13] at M6 ($p < 0.001$) and 5mg [0-9] at last visit of follow up. Three out of the seven patients receiving concomitant csDMARDs were able to withdraw these therapies at M6.

TCZ retention rate

After a median follow-up of 31 months [21-56], 13 (43%) patients were still receiving TCZ and maintained remission. Seventeen (57%) remaining patients discontinued TCZ due to side effects, failure, and/or relapse (n=12) or after achieving remission (n=5) (**Table 2, 3 and 4**).

Safety

Under TCZ therapy, mild to moderate side effects were observed in 6 (20%) patients and included skin rash (n=2), worsening of muco-cutaneous 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- α agents, there is still need for alternative therapies, as up to 35% of patients are refractory, intolerant or present contraindications to these agents (10). Therefore, unmet therapeutic needs in BD have drawn recent attention to biological agents targeting cytokines other than TNF- α (10). IL-6 seems to play a pivotal role in BD, and TCZ represents a possible new therapeutic strategy (11). Currently, the TCZ experience is limited in BD and even if it seems effective in case-series, conflicting results were obtained in muco-cutaneous and/or articular disease manifestations.

Herein, we reported the largest experience of TCZ in refractory BD patients. Ninety percent of our BD patients were refractory or intolerant to anti-TNF- α agents. TCZ was administered intravenously in most of our patients. We could evaluate TCZ efficacy in 3 main BD phenotypes such as uveitis, neurological and muco-cutaneous and articular manifestations. The main conclusions drawn by this study are 1) TCZ seems an effective alternative to anti-TNF- α agents in BD patients with refractory uveitis and neurological manifestations, and 2) The efficacy of TCZ seems less clear in muco-cutaneous and articular phenotype.

In a systematic literature review, Akiyama et al analysed the outcomes of TCZ in 47 refractory patients 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 muco-cutaneous and articular forms (26).

Recent case reports have indeed highlighted the diversity of response rates to TCZ among the different disease clusters confirming a good efficacy in ophthalmological, neurological and vascular disease with conflicting results for the articular and muco-cutaneous phenotype (15-21, 25-29) (**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 macular edema in 88% of cases and on retinal vasculitis in 84% of subjects. This was in agreement with recent studies of TCZ in BD uveitis (21,27) (**Table 5**). Atienza Mateo et al highlighted efficacy of TCZ (CR 63%, PR 19%) in 16 patients with BD uveitis who did not respond to conventional and anti-TNF- α agents (**Table 5**). Ozturk et al reported 5 patients refractory to conventional, interferon- α and anti-TNF- α agents and sight threatening BD uveitis achieving CR in all cases with TCZ treatment (**Table 5**). Leclercq et al. compared TCZ and anti-TNF- α agents in refractory uveitic macular edema, showing TCZ superiority (28). Many other single case reports or limited case series showed the efficacy of TCZ in ocular BD manifestations (18,19,29,30).

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

We could not evaluate the efficacy of TCZ in vascular BD because none of our patients was treated for vascular attempt. TCZ showed good results in vascular BD in a recent chinese study, in which 9 out of the 10 patients with vascular BD obtained a clinical response (CR 50%, PR 40%) (35) (**Table 5**). Ding et al. reported a cohort of seven vascular BD patients refractory to GC and csDMARDs, achieving a clinical response with TCZ (CR 42%, PR 42%, and one patient non evaluable due to premature discontinuation for financial issues) (20) (**Table 5**).

Reports on the effects of TCZ on mucocutaneous and articular lesions are contradictory (13-15,17-19,30-32). Among our muco-cutaneous and articular cluster, we obtained lower remission rate as compared to other clinical phenotypes. In the literature, TCZ had few effects on oral ulcerations in some case series (21,22,36). Worsening of muco-cutaneous lesions after TCZ has also been reported, sometimes requiring drug discontinuation (17,23,37). IL-6 in fact is an important key-factor in wound healing, so its decrease may impair cutaneous and mucosal healing process (38).

For joints manifestations of BD, literature results on TCZ are also conflicting. In the series by Atienza Mateo et al, 4 out of 7 patients improved, with a CR in 2 cases (21). In contrast, many other reports pointed out the failure of TCZ on articular symptoms (19,23). In line with these previous experiences, our data show poor efficacy of TCZ on joint manifestations in BD. One patient in our study, with muco-cutaneous and articular disease also presented renal AA amyloidosis and obtained a CR under TCZ. Two cases of BD secondary renal AA amyloidosis treated with TCZ have been reported in the literature, and in both cases a CR was obtained (39,40). Lastly, TCZ was effective in sparing GC in our series and in published case reports (20,31,35) (**Table 5**).

We do not report new safety signals of TCZ. Common side effects of TCZ such as neutropenia, thrombocytopenia, dyslipidaemia, increased transaminases level and upper respiratory tract infections were observed in 30% of our BD patients in line with previous reports (41). We evidenced 2 severe sepsis requiring treatment interruption including a patient presenting an intestinal perforation which is a well-known drug-related side effect (42,43).

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

In conclusion our study provides the results of the largest cohort of refractory BD patients treated with TCZ.

Ninety percent of BD patients were refractory or intolerant to anti-TNF- α agents. We highlighted that TCZ seems an effective alternative to anti-TNF- α agents in BD patients with refractory uveitis and neurological manifestations. Further prospective studies are warranted to confirm these results.

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Table 1. Demographic and clinical features of BD patients (n=30)

Table 2. Efficacy and safety of tocilizumab in BD patients

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

Table 4. Outcomes of BD patients treated with tocilizumab for neurological or muco-cutaneous and/or articular manifestations

Table 5. Case series of BD patients treated with tocilizumab

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Table 1. Demographic and clinical features of BD patients (n=30)

Female, n (%)	17 (57)
Age at diagnosis (years), median (IQR)	30 [24-33]
HLA-B51 positivity, n (%)	14 (74)
Clinical manifestations	n (%)
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 Tocilizumab	
Number of lines of treatment, median (IQR)	3 [2-4]
Conventional immunosuppressants	n (%)
Azathioprine	13 (48)
Methotrexate	8 (30)
Cyclophosphamide	8 (30)
Interferon α	8 (30)
Cyclosporine	5 (19)
Mycophenolate	2 (7)

Tacrolimus	1 (4)
Biologic agents	n (%)
Adalimumab	18 (67)
Infliximab	17 (63)
Anakinra	5 (19)
Golimumab	3 (11)
Etanercept	2 (7)
Ustekinumab	2 (7)
Certolizumab	1 (4)
Canakinumab	1 (4)

Abbreviations : BD, Behçet disease ; n, number ; IQR, interquartile range ; HLA, human leucocyte antigen

Table 2. Efficacy and safety of tocilizumab in BD patients

BD duration (month), median (IQR)	106 [32-172]
Indication of TCZ	n (%)
Uveitis	18 (60)
Neurological	5 (17)
Muco-cutaneous and/or articular	7 (23)
TCZ treatment	
Intravenous, n (%)	23 (77)
Subcutaneous, n (%)	7 (23)
Combined glucocorticoids, n (%)	27 (90)
Daily dose of glucocorticoids (mg), median (IQR)	20 [10-40]
Combined immunosuppressants, n (%)	7 (26)
TCZ treatment duration (month), median (IQR)	21 [8-38]
Follow up duration (month), median (IQR)	31 [21-56]
Overall Response	n, (%)
Complete response	18 (60)
Partial response	7 (23)
Non-response	5 (17)
Relapse	2 (8)
Safety	n, (%)
Any adverse events	9 (30)
Serious adverse events	3 (10)
Pneumonia	1 (3)
Digestive perforation	1 (3)

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Sepsis	1 (3)
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Abbreviations : BD, Behçet disease ; n, number ; IQR, interquartile range ; TCZ, Tocilizumab

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

Patient	Sex/Age	Prior immunosuppressive drug	Associated immunosuppressive drug	Main symptoms	Other symptoms	Response at M6	Corticosteroids baseline / M6	Relapse	Side effects
1	F/33	ADA, IFX, MTX	–	Uveitis, retinal vasculitis	Oral ulcers, genital ulcers, erythema nodosum, arthralgia, gastrointestinal involvement	Complete response	0/0	–	–
2	F/16	ADA, GLM	–	Uveitis, retinal vasculitis	Oral ulcers, genital ulcers, pseudofolliculitis, Erythema nodosum, Arthralgia	Complete response	20/0	–	–
3	F/29	AZA, ADA, MTX, IFX	MTX	Uveitis, macular edema	Oral ulcers, cartotide arterial aneurysm	Complete response	20/9	–	–
4	F/65	IFN- α , ADA	–	Uveitis, macular edema	Oral ulcers, arthralgia	Complete response	15/5	–	Neutropenia
5	F/24	AZA, IFN- α , ANK, IFX	–	Uveitis, retinal vasculitis, macular edema	Oral ulcers, arthralgia	Complete response	15/10	–	–
6	M/21	IFN- α	–	Uveitis, retinal vasculitis, macular edema	Oral ulcers, pyoderma gangrenosum	Partial response	35/NA	–	Skin rash

7	F/26	AZA, ADA	-	Uveitis, retinal vasculitis	Oral ulcers, genital ulcers, pseudofolliculitis, hidradenitis suppurativa, arthralgias	Complete response	15/5	-	-
8	M/9	ADA, MTX	-	Uveitis	Oral ulcers	Partial response	5/0	-	-
9	M/27	CYC, IFX, ADA, GLM	-	Uveitis, retinal vasculitis, macular edema	arthralgias	Complete response	20/15	Yes	-
10	M/24	IFX, ADA, AZA	-	Uveitis, retinal vasculitis	Oral ulcers, genital ulcers, arthralgias	Partial response	10/10	Yes	-
11	M/29	CYC, IFN- α , IFX, MMF, ADA, ANK, MTX	-	Uveitis, retinal vasculitis	Oral ulcers, pseudofolliculitis	Non- response	40/NA		-
12	F/32	AZA, CYC, IFN- α , ANK, IFX	-	Uveitis, macular edema	Oral ulcers, genital ulcers, pseudofolliculitis, arthralgia, venous thrombosis, pericarditis	Complete response	10/9	-	Recurrent urinary tract infections
13	M/31	Yes but NA	NA	Uveitis, retinal vasculitis	Oral ulcers	Complete response	40/15	-	-
14	M/32	Yes but NA	NA	Uveitis, retinal vasculitis	Oral ulcers, pseudofolliculitis, arthralgias	Complete response	80/16	-	-

15	M/29	Yes but NA	NA	Uveitis, retinal vasculitis	Oral ulcers, pseudofolliculitis	Non- response	70/NA		-
16	M/22	AZA, IFX, ADA, CYC	Yes but NA	Uveitis, macular edema	Oral ulcers, papulopustular lesions, erythema nodosum	Non- response	64/48		-
17	F/48	IFX, ADA	-	Uveitis, macular edema	Oral ulcers, genital ulcers, pseudofolliculitis, arthralgia	Complete response	20/9	-	Dyslipidemia
18	M/32	ADA	-	Uveitis, retinal vasculitis	Oral ulcers, pseudofolliculitis, arthralgias	Complete response	80/8	-	-

Abbreviations: M6, month 6 after TCZ beginning; N, none; F, female; M, male; NA, not available; ADA, adalimumab; IFX, infliximab; MTX, methotrexate; GLM, golimumab; AZA, azathioprine; INF- α , interferon α ; ANK, anakinra ; CYC, cyclophosphamide ; MMF, mycophenolate mophetil

Table 4. Outcomes of BD patients treated with tocilizumab for neurological or muco-cutaneous and/or articular manifestations

Patient	Sex/Age	Prior immunosuppressive drug	Associated immunosuppressive drug	Main symptoms	Other symptoms	Response at M6	Corticosteroids baseline / M6	Relapse	Side effects
1	F/33	AZA, IFX, ADA	-	Neurological BD (meningitis, parenchymal lesions, myelitis, MRI alterations)	Uveitis, oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum, arthralgias	Complete response	0/0	-	-
2	F/24	CsA, MTX, AZA, TCR, IFN- α , CYC, IFX, ADA, CTZ, ANK	Yes but NA	Neurological BD (Optic neuropathy)	Oral ulcers, genital ulcers, arthralgias, gastrointestinal involvement	Partial response	38/14	-	-
3	F/32	CsA, IFX, AZA	-	Neurological BD (meningitis, Parenchymal lesions, MRI)	Oral ulcers, genital ulcers, papulopustular abdominal lesions	Complete response	50/5	-	-
4	M/33	MTX, CYC, MMF, AZA	-	Neurological BD (parenchymal lesions, myelitis, MRI alterations), arthralgias and arthritis	Uveitis, retinal vasculitis, venous thrombosis	Complete response	5/5	-	Pneumonia
5	F/48	AZA, CYC, IFX, INF, 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	Partial remission	50/25	-	Sepsis (TCZ stopped at M30)

						thrombosis, gastrointestinal involvement				
6	F/24	MTX, IFX, ADA	–		Oral ulcers, genital ulcers, arthralgias and arthritis	Uveitis, retinal vasculitis, macular edema	Partial response	23/15	–	Sepsis with digestive perforation (TCZ stopped at M9)
7	F/34	GLM, ADA	–		Oral ulcers, genital ulcers, pseudofolliculitis, arthralgias and arthritis	Venous thrombosis, gastrointestinal involvement	Partial response	10/8	–	–
8	F/20	AZA, IFX, USTEK	USTEK		Oral ulcers, genital ulcers, pseudofolliculitis, pyoderma gangrenosum	Gastrointestinal involvement	Complete response	20/8	–	–
9	F/36	CsA, IFX, ANK, CYC, USTEK	USTEK		Oral ulcers, pyoderma gangrenosum, arthralgias	–	Complete response	10/0	–	–
10	M/27	AZA, MTX, IFX, ADA, ETN, CYC, CsA, CNK, IFN- α	–		Oral ulcers, genital ulcers, pseudofolliculitis, arthralgias	–	Non- response	3/0		Worsening of muco- cutaneous manifestations (TCZ stopped at M2)
11	F/43	MTX, ADA, ETN	Yes but NA		Oral ulcers, genital ulcers, erythema nodosum, arthralgias and arthritis	Gastrointestinal involvement, myocarditis	Non- response	25/NA		Skin rash (TCZ stopped at M3)
12	M/40	–	–		Renal AA amyloidosis papulopustular	Oral ulcers, genital ulcers, papulopustular	Complete response	0/0	–	–

lesions,
arthralgias

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Abbreviations: BD, Behçet disease; M 2-3-6-9-30, month 2-3-6-9-30 after tocilizumab initiation; N, none; F, female; M, male; NA, not available; MRI, magnetic resonance imaging ; AZA, azathioprine; IFX, infliximab; ADA, adalimumab; CsA, cyclosporine; TCZ, tocilizumab; MTX, methotrexate; TCR, tacrolimus; INF- α , interferon α ; CYC, cyclophosphamide; CTZ, certolizumab; ANK, anakinra; MMF, mycophenolate mophetil; GLM, golimumab ; USTEK, ustekinumab ; CNK, canakinumab ; ENT, etanercept .

Table 5. Case series of BD patients treated with Tocilizumab

Reference	n	Clinical manifestations (n)	Previous treatments (n)	TCZ indication (n)	TCZ way of administration (IV or SC) (n)	TCZ associated treatments (n)	Clinical outcomes (n)	Prednisone (daily dose, mg) (Baseline to M6)	SAEs (n)	Median follow-up under TCZ (months)	Relapse (month of TCZ therapy)
Zhong (35)	10	Vascular disease (10), arterial (10), venous (2), mucocutaneous (10), GI (1), uveitis (1), joints (2).	GCs (10), CYC (7), MMF (2), AZA (2), TCR (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]*	1 (7)
Ding (20)	7	Vascular disease (7): arterial (7), venous (2)	GCs (7), CYC (7), AZA (5), MTX 2), TCR (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%) #	27 +/-17 to 9+/-3	None	19 [4-33]*	None
Atienza-Mateo (21)	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), GLM (3), CNK (1), CTZ (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%), #. Joints : CR (29%), PR (29%), NR (43%)	NA	Severe infusion reaction (1), cellulitis with sepsis (1)	20 [9-45]	None
Liu (31)	11	Neurological (11), mucocutaneous (11), uveitis (3), joints (2), vascular (2).	GCs (11), CYC (8), AZA (6), MTX (5), CsA (2), TCR (1), MMF (1), intrathecal	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 +/-10	2 (8;18)

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		injection of dexamethasone and MTX (5), IFX (5), IFN-α (3), daclizumab (1)											
		GCs (5), AZA (5), CsA (4), IFN-α (5), IFX (5), ADA (2), MMF (1), PSTA injections (2), IVDEX injection (4), bevacizumab ocular injection (1)	Uveitis (5): CME (4), RV (3)	IV (5)	Oral GCs (3), AZA (2), CsA (1), IVDEX injection (1)	Uveitis: CR (100%); CME: CR (75%), PR (25%); RV : CR (100%)	NA	None	11 [5-19]	None			
Ozturk (27)	5	Uveitis (5) and vascular disease (1).											
		Oral ulcers (28), genital ulcers (16), skin lesions (22), uveitis (21), joints (19), vascular disease (6), neuro-Behçet (5), gastrointestinal involvement (6), AA amyloidosis (1)	GCs (28), ADA (18), IFX (17), AZA (13), MTX (8), GLM (3), INF (8), ANK (5), CYC (8), CsA (5), TCR (1), CTZ (1), USTEK (2), ETN (2), CNK (1), MMF (2)	Uveitis (18), neurological BD (5), muco-cutaneous and/or articular (7),	GCs (28), DMARDs (7)	Neurological: CR + PR (100%), CR (60%), PR (40%) Muco-cutaneous and/or articular: CR + PR (71%), CR (42%), PR	20 to 9	Pneumonia (1), Sepsis (1), infection with digestive perforation (1)	21 [8-38]	2			
Khitri	30			IV (23), SC (7)									

*Median follow-up in month (TCZ therapy and post therapy follow-up)

#One patient was not evaluable due to premature drug discontinuation

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Abbreviations: n, number; TCZ, tocilizumab; M6, month 6 after tocilizumab initiation; CR, complete response; PR, partial response; NR, non-response; IV, intra venous; SC sub-cutaneous; ADA, adalimumab; ANK, anakinra; AZA, azathioprine; CME, cystoid macular oedema; CNK, canakinumab; COL, colchicine; CsA, cyclosporine A; CTZ, certolizumab; CYC, cyclophosphamide; ETN, etanercept; GCs, glucocorticoids; GLM, golimumab; IFX, infliximab; INF- α 2a, interferon α 2a; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; ; USTEK, ustekinumab ;PSTA, posterior subtenon triamcinolone acetonide; RV, retinal vasculitis; SAEs, severe adverse events; TCR, tacrolimus; THD, thalidomide; TCZ, tocilizumab.