Review

IL-6 blockade for Behçet's disease: review on 31 anti-TNF naive and 45 anti-TNF experienced patients

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ABSTRACT

Objective. *Despite the remarkable efficacy of anti-TNF agents in Behçet's disease (BD), unmet therapeutic needs for refractory or intolerant patients to these drugs still exist. Based on evidence implicating IL-6 in the pathogenesis of BD, we summarise the current experience on the off-label administration of the anti-IL-6 receptor antibody tocilizumab for BD refractory to disease-modifying anti-rheumatic drugs.*

Methods. *We searched PubMed and EMBASE for original articles published through December 2021 reporting on the use of tocilizumab for BD.*

Results. *We retrieved 25 articles fulfilling our search criteria, reporting on a total of 74 patients of whom 31 were anti-TNF naive; 2 additional anti-TNF experienced patients were included. The vast majority (72 of 76) received the standard intravenous dose of tocilizumab, whereas the total follow-up, including also post-treatment follow-up in many patients, ranged from 2 to 84 months without new safety issues. Tocilizumab was given in anti-TNF naive patients predominantly for vascular (n=16), central nervous system (n=7) and ocular involvement (n=5). On the other hand, anti-TNF experienced patients received tocilizumab predominantly for ocular (n=28), central nervous system (n=8) and mucocutaneous involvement (n=6). Tocilizumab was effective in 87% of anti-TNF naive (13 and 14 with complete and partial remission, respectively) and in 80% of anti-TNF experienced patients (17 and 19 with complete and partial remission, respectively).*

Conclusion. *Although preliminary, evidence published so far suggests that IL-6 inhibition is a legitimate therapeutic option for BD patients with refractory ocular, CNS and vascular involvement. Controlled studies are clearly needed.*

Introduction

Behçet's disease (BD) is a systemic inflammatory disorder of unknown aetiology that is classified among the vasculitides (1). The disease is characterised by the presence of recurrent oral ulcers along with other clinical manifestations, such as genital ulcers, arthritis, pustular skin lesions, panuveitis, neurological, gastrointestinal, arterial and venous involvement, with potentially severe morbidity (2). Due to the differences in severity and type of affected organ systems, treatment is individualised and prompt initiation of immunosuppressants is mandatory in case of vital organ involvement. For these patients, conventional DMARDs, such as azathioprine, cyclosporine-A, methotrexate, interferon-α and cyclophosphamide, combined or not with corticosteroids, had long been used (3). During the last 20 years, anti-TNF agents were proven effective in treating essentially every clinical manifestation of BD and their use is recommended as first-line in patients with severe ocular or CNS involvement (4, 5). Despite their remarkable efficacy there is still need for alternative therapies, as many patients are refractory or intolerant to established treatments or present contraindications. Therefore, other biologic agents have been utilised for treating such cases and the results are rather encouraging (6).

Tocilizumab (TCZ) is a humanised antibody targeting the membrane IL-6 receptor, that is currently approved for the treatment of rheumatoid arthritis and giant cell arteritis (7), and is recommended for patients with systemic sclerosis-associated interstitial lung disease (8). The use of TCZ in BD is based on evidence implicating IL-6 in pathogenesis. For example, IL-6 levels are elevated in the serum of patients

with active BD and correlate with disease activity and arthritic manifestations (9, 10). Moreover, IL-6 activity is elevated in the cerebrospinal fluid of patients with neuro-Behçet's syndrome and seems to be a marker of disease activity in these patients (11, 12). IL-6 concentration is also elevated in vitreous fluids of patients with autoimmune uveitis and is thought to contribute to ocular inflammation, due to IL-6-dependent Th17 differentiation (13). Elevated IL-6 levels are also considered responsible for an increase of Th17 cells seen in patients with BD, which is combined with a reduction of the T-regulatory cells (14).

Herein, we summarise the published experience regarding the use of the anti-IL-6 receptor antibody TCZ in patients with BD and try to critically review its effectiveness in different clinical manifestations.

Material and methods

We searched the Medline/PubMed and Embase databases for primary articles published in English through December 2021, reporting on the therapeutic use of the biological agent TCZ, targeting IL-6 cytokine, in patients with BD. Search terms included: "Behçet's" in combination with "tocilizumab". We included case reports, case series and research studies, whereas systematic reviews, meta-analyses, comments and duplicate studies, as well as studies involving patients with autoimmune uveitis that did not present results for BD patients separately, were excluded. Papers and abstracts presented in conferences were not considered. Regarding treatment outcomes, BD patients responding to TCZ treatment were considered as having "complete remission" when disappearance of symptom(s) was explicitly stated by the authors; all other responding patients were considered as having "partial remission".

Results

We retrieved 25 articles (Fig. 1), involving a total of 74 patients, on the use of TCZ in BD, that fulfilled our search criteria (15-39). Of them, only one was a prospective study examining the efficacy of TCZ on refractory arterial involvement in 10 patients with BD (31). Two studies were retrospective, concerning 19 patients overall: three who received TCZ for uveitic macular oedema, 14 for ocular involvement and 2 for CNS involvement. (29, 32) The remaining 22 articles were case reports or case series on different BD manifestations. Two additional patients with BD from our centre were also included. Most common reasons for TCZ administration were ocular involvement in 33/76 patients (including one in whom TCZ was also administered for neuro-BD), followed by vascular involvement in 17 and neuro-BD in 15 patients. Four patients had various BD symptoms (oral and genital ulcers, skin, fever, arthralgias), three had mucocutaneous manifestations, two had secondary to BD renal AA amyloidosis and one patient each had intestinal BD and MAGIC syndrome.

TCZ was administered intravenously in 72 and subcutaneously in 4 patients. All included patients were either inadequately controlled with, or intolerant to, conventional immunosuppressive regimens, such as combinations of corticosteroids with azathioprine, cyslosporine-A, methotrexate, mycophenolate mofetil, tacrolimus or with cyclophosphamide. TCZ was either administered in combination with corticosteroids or csDMARDs. Thirty-one patients were anti-TNF naive (Table I) and 45 had received at least one anti-TNF agent prior to TCZ treatment (Table II). Reasons for not having been treated with a TNF inhibitor, if reported, were either contraindications, such as history of malignancy, poor cardiac function or a positive mycobacterium tuberculosis test or physician's choice, due to elevated inflammatory markers or renal AA amyloidosis.

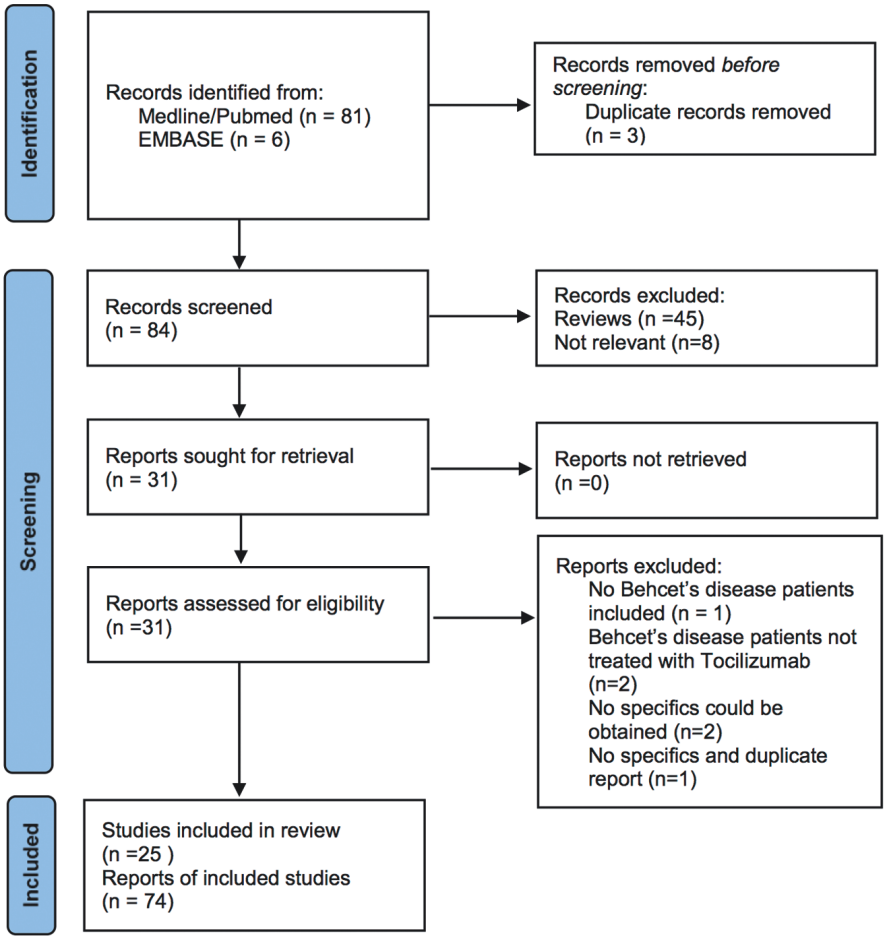

Fig. 1. PRISMA flow chart illustrating the search strategy and study inclusion.

Efficacy in anti-TNF naive patients

Overall, 10 studies reported on 31 anti-TNF naive patients who received TCZ

Table I. Disease characteristics and outcomes after treatment with tocilizumab in 31 anti-TNF naive patients with Behcet's disease.

Study	No of patients	Gender, Age	Previous treatment	Target clinical manifestations	Other clinical manifestations	Concomitant treatment	Clinical outcome	AEs	Follow up period
Redondo-Pachon, 2013 (33)	1	F, 51	CS low dose for 16 years	Secondary renal AA amyloidosis	None (History of OU, GU, EN and iridocyclitis)	Colchicine	Complete response. Decrease of proteinuria and CRP after 2nd infusion.	None	12 months
Terreaux, 2015 (17)	1	F, 37	CS, colchicine	MAGIC syndrome-chondritis	OU, GU, S, fever	CS	Failure. Recurrence of OU, S and chondritis	None	4 months
Alokaily 2017 (21)	1	M, 33	CS, Interferon β,	BD uveitis	OU, GU, EN, S, neurological manifestations	CS	Partial response. (improvement of VA, reduction of vitritis, resolution of vasculitis)	None	2 months
Essaadouni 2017 (22)	1	F, 26	CS, AZA, Colchicine, CYC	Neuro-BD	fever	CS	Complete remission (clear regression of all lesions of brain MRI, discontinuation of CS from 15mg/d)	None	21 months
Ding, 2018 (26)	6	M/F: 5/1, 31.3±8.9	CS, MTX, AZA, CYC, LEF	Vasculo-BD	OU, GU, S	CS, MTX, AZA, CYC, LEF	Complete remission in 2, partial remission in 4. (Radiologic improvement of artery stenosis in one patient, reduction of mean CS dosage from 27.1±16.5 mg/d to 8.9±3.2 mg/d)	None	4-24
Ilbay, 2019 (25)	1	M, 58	Colchicine	Secondary renal AA amyloidosis	None (History of OU, GU, EN, S)	Colchicine	Partial remission. Decrease of proteinuria after the 2nd infusion.	None	29 months
Liu, 2020 (28)	5	M/F:4/1, 34.6±6.7	CS, MTX, AZA, CsA, CYC, MMF	Neuro-BD	OU, GU, S, A, uveitis	CS, MTX, AZA, CYC	All had partial remission (clear regression of MRI lesions in 1, improvement in 3,stable in 1) Reduction of CS dosage from 69.2±16.9 mg/d to 16.4 ± 16.2 mg/d, withdrawal in 3)	None	2-14 months
Atienza-Mateo 2021 (29)	2	M, 27 M,45	MTX, CsA, CYC Colchicine, MTX, AZA	Uveitis Neuro-BD	-- Panuveitis, OU, GU, A, DVT	MTX AZA	Complete remission Complete remission	None	60 months 64 months
Zhong, 2021 (31)	10	All male, 44.3±10.5	CYC, MMF, TAC, AZA, CS	Arterial involvement	OU (10), GU (4), S (8)	CS, MMF, CYC, AZA, TAC	6 had complete response, 3 partial response, 1 relapse. (radiologic improvement of arterial lesions in 4, reduction of mean CS dose from 54.5±20.6 mg/d to 8.3±3.6 mg/d)	Mild respiratory tract infection	24 weeks
Leclercq, 2021 (32)	3	F, 47 M, 25 M, 31	Not specified Not specified Not specified	Uveitic macular oedema	S, A, cardiac, bilateral uveitis OU, GU, S, A OU, S, bilateral uveitis	CS CS CS	Complete remission Partial remission but relapsed No response	None	16 months Not specified 4 months

M: male; F: female; OU: oral ulcers; GU: genital ulcers; S: skin lesions; EN: erythema nodosum; A: arthritis, CS: corticosteroids; CYC: cyclophosphamide; MMF: mycophenolate mofetil; TAC: tacrolimus; MTX: methotrexate, CsA: cyclosporine A; AZA: azathioprine; LEF: leflunomide; CRP: C-reactive protein.

for ocular involvement (n=5), neuro-BD (n=7, one also had panuveitis), vascular involvement (n=16), secondary renal AA amyloidosis (n=2) and MAGIC syndrome (n=1) (17, 21, 22, 25, 26, 28, 29, 31-33) (Table I).

All patients had previously been treated with corticosteroids combined with various immunosuppressants, except of one patient who had only received low-dose corticosteroids. One patient who received TCZ for BD uveitis, had also been treated with interferon β, as he also presented neuro-BD and was misdiagnosed as multiple sclerosis. TCZ was effective in all patients, except two: one patient who received TCZ for chondritis due to MAGIC syndrome and one for uveitic macular oedema (17, 32). More specifically, TCZ induced remission in all patients with ocular and neurological manifestations, including one with both ocular and neuro-BD. One patient with bilateral panuveitis and uveitic macular oedema, although he initially had a partial response to TCZ, experienced a relapse and had to discontinue treatment (32). Two patients with neuro-BD had complete remission of neurologic symptoms, and one was able to discontinue concomitant corticosteroids. TCZ ameliorated radiographic imaging in at least three patients with CNS involvement, with clear regression in two of them (22, 28). In the only prospective study involving 10 anti-TNF naive BD patients with refractory arterial involvement, TCZ achieved complete and partial remission in 6 and 3 patients respectively, with radiologic improvement in 3 of them. The remaining patient relapsed,

Table II. Disease characteristics and outcomes after treatment with tocilizumab in 45 anti-TNF experienced patients with Behcet's disease.

Study	No of patients	Gender, Age	Previous treatment	Target clinical manifestations	Other clinical manifestations	Concomitant treatment	Clinical outcome	AEs	Follow up period
Hirano, 2011 (15)	1	F, 47	CS, colchicine, CsA, IFX	BD uveitis	OU, GU, EN	None	Partial response (improvement of VA and BDCAF score)	Transient increase of LDL cholesterol	12 months
Shapiro, 2012 (16)	1	M, 30	CS, MTX, AZA, CsA, CYC, MMF, IFN, daclizumab, IFX	Neuro-BD	Uveitis	CS	Complete response. Recurrence of oral ulcers (clear regression of brain MRI lesions, withdrawal of CS)	None	7 months
Urbaniak, 2012 (27)	1	M, 46	CS, Colchicine, AZA, IFX	Neuro-BD	Low fever, malaise, arthralgias	CS, AZA	Partial response (clear regression of MRI lesions of the spine, reduction of CS from 1mg/kg/d to 15mg/d)	Scrotal abscess – discontinuation of TCZ	8 months
Diamantopoulos, 2013 (34)	2	F, 55 F, 26	CS, MTX, AZA, colchicine, ETN, IFX CS, CsA, colchicine, AZA, MTX, IFX, ADA	OU, GU, S OU, GU	-- --	AZA	Worsening of mucocutaneous lesions Recurrence of GU	None	1 month 3 months
Caso, 2013 (35)	1	F, 41	CS, AZA, CsA, ADA, IFX, ANA, Colchicine, CYC, MTX	OU, GU, fever, pemphigo, uveitis, EN, arthralgias	--	CS	Complete response	None	14 months
Cantarini, 2014 (36)	1	F, 43	CS, Colchicine, CsA, MTX, CYC, IFX	OU, A	No	Not specified	Worsening of OU, GU and occurrence of skin lesions	None	2 weeks
Calvo-Rio, 2014 (37)	2	F, 42 F, 67	CS, MTX, CsA, AZA, ADA, GLM CS, MTX, CsA, IFX, ADA	BD uveitis	Not specified	CS CS	Partial response (improvement of VA) Complete response (stable VA)	None	1 12
Addimanda, 2015 (38)	3	F, 27 F, 48 F, 36	CS, AZA, colchicine, IFX, tacrolimus CYC. CS, AZA, CYC, IFX, IFN-α, chlorambusil. CS, CsA, IFX	Neuro-BD	OU, GU, fever	CS	Partial response (stable brain MRI, reduction of CS from 50mg/d to 15 mg/d) Partial response (stable brain MRI, reduction of CS to 25 mg/d) Partial response	Drop of leukocytes and neutrophils in one patient	26 months 26 months 26 months
Papo, 2014 (39)	1	M, 40	CYC, MMF, IFNα, IFX, ADA	BD uveitis	Not specified	CS	No response	None	6 months
Deroux 2016 (18)	4	F ,23 F, 31 F, 39 F, 41	CS, AZA, CsA, IFNα, IFX, ADA, ANA. CS, AZA, CsA, ADA, GLM. CS, AZA, ADA, GLM CS, MTX, IFX, ADA	BD uveitis BD uveitis Mucocutaneous, A, GI BD uveitis	OU, GU, arthralgias, GI. OU, GU, S, A, uveitis. OU, GU, S, A, GI. OU, GU, A, GI	CS CS CS CS	Partial remission (improvement of VA reduction of CS from 30mg/d to 10mg/d) Partial remission (improvement of VA reduction of CS from 20mg/d to 5mg/d) Partial remission- persistence of joint symptoms (reduction of CS from 20mg/d to 10mg/d) Partial remission-persistence of joint symptoms (reduction of CS from 20mg/d to 5mg/d)	None None Recurrent labial herpes None	12 months
Emmi, 2016 (19)	1	M, 35	Colchicine. AZA, CsA, MTX, IFX, ADA, ETN, ANA, CANA, IFN-α	Arthralgias, acute confusional state	None (History of OU, GU, S, superficial venous thrombosis)	Not specified	Recurrence of major oral ulcers.	None	2 months
Santos-Gomez, 2016 (20)	2	Not specified	ADA, GLM ADA, IFX	BD uveitis	Not mentioned	Not specified	Complete remission	None	Not specified
Chen, 2017 (23)	1	M, 30	CS, thalidomide, IFX, SFZ, ADA, ETN	Intestinal BD	OU, GU, S	CS, AZA, thalidomide	Partial remission (improvement of endoscopy images and discontinuation of CS from 1mg/kg/d)	None	9
Ozturk, 2017 (24)	5	M/F:2/3, 25.4±3	CS, AZA, CsA, IFNα, IFX, ADA	BD uveitis	Not mentioned	CS, AZA, CsA	Partial remission in all (improvement of VA in 4, reduction of CS dose in 2 from 30mg/d to 5mg/d and 20mg/d to 5mg/d and stable dose of 5mg/d in 1)	Slightly elevated cholesterol level in one patient	5-27

Study	No of patients	Gender, Age	Previous treatment	Target clinical manifestations	Other clinical manifestations	Concomitant treatment	Clinical outcome	AEs	Follow up period
Ding, 2018 (26)	1	M, 42	CS, MTX, AZA, CYC, tacrolimus, ETN	Vasculo-BD	OU, S	CS, AZA	Complete remission (Radiologic improvement of arterial stenosis, reduction of mean CS dosage from 27.1±16.5 mg/d to 8.9±3.2 mg/d)	None	33
Atienza-Mateo 2021 (29)	14	M/F: 8/6 41.7±19.1	Colchicine, Thalidomide, MTX, CsA, AZA, CYC, MMF, IFX, ADA, ETN, GLM, CANA	Uveitis and/or neuro-BD	OU, GU, A, S,	MTX, CsA, AZA, MMF, CS	Complete remission of uveitis in 8/14 patients and of neuro-BD in 2/4 patients. Response 2/10 of mucocutaneous lesions and 4/7 of arthritis.	Infusion reaction in 1 patient-discontinuation of TCZ cellulitis with sepsis in1-temporal withdrawal	Median 20 months (1-64)
Karabulut, 2021 (30)	2	M, 32 M, 36	AZA, IFX, CS AZA, IFX, CS	Neuro-BD Neuro-BD	OU, GU, S OU, GU, A	CS CS	Complete remission (complete regression of cranial MRI, reduction of CS from 20mg/d to 2.5 mg/ every-other-day) Complete remission (complete regression of cranial MRI)	None	6 months 4 months
Sfikakis, unpublished	2	F, 61 F, 64	Cs, CsA, AZA, CYC, IFX, ADA CS, AZA, MTX, CsA, CYC, IFX, ADA, ANA	Neuro-BD, pyoderma gangrenosum. Uveitis	OU	AZA, CS	Complete remission No response	None None	84 months 2 months

M: male; F: female; OU: oral ulcers; GU: genital ulcers; S: skin lesions; EN: erythema nodosum; A: arthritis; GI: gastrointestinal; CS: corticosteroids; CYC: cyclophosphamide; MMF: mycophenolate mofetil; TAC: tacrolimus; MTX: methotrexate; CsA: cyclosporine A; AZA: azathioprine; SFZ: sulfasalazine; IFX: infliximab; ADA: adalimumab; ETN: etanercept; GLM: golimumab; CANA: canakinumab; ANA: anakinra; IFN-α: interferon-α; CRP: C-reactive protein.

as he experienced abdominal aortic aneurysm enlargement. Moreover, there was a significant amelioration of oral ulcers and complete remission of cutaneous lesions in all 8 patients with skin involvement, reduction in concomitant corticosteroid dosage in all 9 patients, as well as of inflammatory markers and BSAS and BCAF (31). Similarly, in a case series involving 6 anti-TNF naive patients with vascular BD, 2 had complete and 3 had partial response to TCZ therapy, one with radiological improvement. The remaining patient, while responsive, discontinued treatment due to economic burden, thus could not be evaluated.

Significant reductions in mean glucocorticosteroid dosage and immunosuppressants, as well as in inflammatory biomarkers were observed (Table I) (26, 28, 31). TCZ was effective in remitting renal AA amyloidosis secondary to BD in two patients with no active BD, as proteinuria and inflammatory markers decreased rapidly after the 2nd infusion and serum creatinine levels remained stable (25, 33). As mentioned above, TCZ failed to treat a patient with MAGIC syndrome, who had previously received colchicine with remission of mouth ulcers. TCZ was initiated due to persistence of chondritis, however 4 months after treatment initiation there was recurrence of mouth ulcers, pseudofolliculitis as well as chondritis. TCZ was withdrawn and Infliximab was initiated leading to complete remission (17).

Efficacy in anti-TNF experienced patients

Disease characteristics of anti-TNF experienced BD patients treated with TCZ are shown in Table II. All reports came from single case reports or case series, except for one multicentre retrospective study. TCZ was either administered as monotherapy, only with corticosteroids, or combined with conventional DMARDs, most frequently azathioprine. Reasons for TCZ initiation were ocular involvement (n=28), CNS involvement (n=8), mainly mucocutaneous symptoms (n=6, including two patients with severe arthritis), arthralgias with confusional state in one patient and intestinal and vascular BD in one patient each (15, 16, 18-20, 24, 26, 27, 29, 30, 34, 35, 37-39).

Of the 45 anti-TNF experienced patients, 20 had received only one anti-TNF agent prior to TCZ treatment (IFX n=14, ADL n=4, ETN n=2), 22 patients had received two anti-TNF agents and three had received three anti-TNF agents. The most frequently used anti-TNF agent was Infliximab, followed by adalimumab, golimumab and etanercept. Other biologic agents administered before TCZ were the anti-IL1 agents anakinra and canakinumab in 5 patients (three received anakinra, one canakinumab and one received both) and daclizumab, an anti-CD25 antibody, which was given in one patient with neuro-BD; 10 of the 43 anti-TNF-experienced patients had also been treated with IFN-α prior to TCZ.

TCZ induced partial or complete remission in 19 and 17 of 45patients, respectively. Regarding ocular involvement, TCZ was effective in all but 4 patients with BD uveitis, one of whom however had an improvement on articular manifestations (29, 39). More specifically, TCZ administration was associated with rapid resolution of ocular inflammation, with reduction of anterior chamber cells, vitritis and macular oedema and

Table III. Disease characteristics and outcomes in BD patients that received tocilizumab for ocular, central nervous system or vascular involvement.

	Study	No of patients	Gender, Age	Characteristics of manifestation	Prior anti-TNF treatment	Clinical outcome of the involvement	Follow up period (months)
Ocular involvement	Hirano, 2011 (15)	1	F, 47	Bilateral posterior uveitis	Yes (IFX)	**PR** (improvement of VA and BDCAF score)	12
	Calvo-Rio, 2014 (37)	2	F, 42 F, 67	Bilateral uveitis, CME in the left eye Bilateral uveitis (vitritis, retinal vasculitis and CME)	Yes (ADA, GLM) Yes (ADA, IFX)	**PR** (improvement of VA) **CR** (stable VA)	1 12
	Papo, 2014 (39)	1	M, 40	Bilateral panuveitis and retinal vasculitis	Yes (IFX, ADA)	**NR**	6
	Deroux 2016 (18)	3	F ,23 F, 31 F, 41	Bilateral posterior uveitis, vascular leakage from retinal vein, retinal leakage at the posterior pole, CME Bilateral posterior uveitis and retinal vasculitis Bilateral panuveitis and retinal vasculitis, CME in right eye	Yes (IFX, ADA) Yes (ADA, GLM) Yes (IFX, ADA)	**CR** (improvement of VA) **CR** (improvement of VA) **CR**	12
	Santos-Gomez, 2016 (20)	2	Not specified	Not specified	Yes (ADA n=2, GLM n=1, IFX n=1)	**CR**	Not specified
	Ozturk, 2017 (24)	5	M/F:2/3, 25.4±3	Bilateral panuveitis, retinal vasculitis (n=4), and CME (n=5), hypopyon (n=1)	Yes (IFX n=5, ADA n=2)	**PR** in all (improvement of VA in 4)	5-27
	Alokaily 2017 (21)	1	M, 33	Bilateral panuveitis, retinal vasculitis	No	**PR** (improvement of VA, reduction of vitritis, resolution of vasculitis)	2
	Atienza-Mateo 2021 (29)	16	10M:6F, 36.5±18.2	12 bilateral /4 unilateral panuveitis (n=11; 5 with retinal vasculitis), anterior (n=3) and posterior (n=2) uveitis. CME (n=9)	Yes in 14/16 (ADA n=10, IFX n=7, GLM n=3, ETN n=1)	**CR** 10/16, PR 3/16	median (IQR)= 20 (9-45)
	Leclercq, 2021 (32)	3	F, 47 M, 25 M, 31	Uveitic macular oedema	Not specified	**CR** **PR and relapse** **NR**	16 Not specified 4
	Sfikakis, unpublished	1	F, 64	Bilateral uveitis	Yes (IFX, ADA)	**NR**	2
Central Nervous System involvement	Essaadouni 2017 (22)	1	F, 26	Spastic hemiparesis, generalised tonic seizures, headache, fever, unilateral exaggerated deep tendon reflexes (positive Babinski sign). Multiple lesions in brain MRI (brain stem, occipital protuberance, thalamus right lens capsule, periventricular white matter, cerebellar hemispheres and semioval centres)	No	**CR** (clear regression of all lesions of brain MRI)	21
	Liu, 2020 (28)	5	M/F:4/1, 34.6±6.7	Headache, urinary incontinence, muscle weakness, fever, numbness, dysarthria, conscious disturbance, visual loss, epilepsy, cognitive dysfunction. Multiple MRI lesions (spinal cord, brainstem, hemicerebrum)	No	**PR** in all (clear regression of MRI lesions in 1, improvement in 3, stable in 1).	2-14
	Shapiro, 2012 (16)	1	M, 30	Recurrent meningo-encephalitis (headaches and fever). Positive MRI: right cerebral peduncle lesion extending into the upper pons.	Yes (IFX)	**CR** (clear regression of brain MRI lesions)	7
	Urbaniak, 2012 (27)	1	M, 46	Neurogenic bladder dysfunction, pyramidal disturbances with numbness distal to the sensory level of Th 7/8, gait disturbance of the right leg with paraparesis and spasticity, hyperreflexia of the arms and low back pain. MRI: signal intensification and atrophy of the spinal cord at the mid and distal thoracic level	Yes (IFX)	**PR** (clear regression of MRI lesions of the spine)	8
	Addimanda, 2015 (38)	3	F, 27 F, 48 F, 36	Optic neuritis, left-sided muscle weakness, unsteady gait, positive pronator drift test on the left, neurogenic bladder, fever. brain MRI: small hyperintense lesion in the right parietal subcortical area. Optic neuritis, paresthesias and muscle weakness in her left arm and lower limbs. headache, urinary incontinence. Brain MRI: optic nerve enhancement, small lesion in the right fronto-basal area Headache, paresthesias, left eye ptosis and diplopia, urinary urgency, dyslalia, slurred speech, memory deficits. Brain CT and MRI: lesions in the mid-brain, spinal cord, left thalamus and insula, left mesencephalon, anterior and lateral aspect of the pons of the left.	Yes (IFX) Yes (IFX) Yes (IFX)	**PR** (stable brain MRI with only a small new lesion) **PR** (stable brain MRI) **PR** (stable brain MRI)	26 26 26

	Study	No of patients	Gender, Age	Characteristics of manifestation	Prior anti-TNF treatment	Clinical outcome of the involvement	Follow up period (months)
	Karabulut, 2021 (30)	2	M, 32 M, 36	Headache, diplopia, visual impairment. Brain MRI: basal nuclear involvement, right thalamus and internal capsule posterior leg, mesencephalon and posterior colliculus involvement. Headaches, visual impairment. Brain MRI: left inferior cerebellar pedicle, left thalamus lateral and left peritrigonal region	Yes (IFX) Yes (IFX)	**CR** (complete regression of cranial MRI) **CR** (complete regression of cranial MRI)	6 4
	Atienza-Mateo 2021 (29)	5	4M:1F, (50,16,75, 45,39)	Optic neuritis (n=2), right hemiparesis (n=1), haemorrhagic stroke (n=1), axonal sensory polyneuropathy, vascular migraine	Yes in 4/5 (ADA n=3, IFX n=2, GLM n=1, ETN n=1)	**CR** 3/5, Stable 2/5	12, 42, 48, 64, 96
	Sfikakis, unpublished	1	F, 61	MS-like syndrome, urinary incontinence	Yes (IFX, ADA)	**CR**	84
Vascular involvement	Ding, 2018 (26)	7	M/F: 6/1, 32.9 ± 9.0	Multiple arterial lesions in all patients (arterial aneurysm n=5, stenosis n=4 and occlusion n=3) Multiple venous thrombosis in two patients.	Yes 1/7 (ETN)	**CR** in 3, **PR** in 3, one patient could not be evaluated (Radiologic improvement of artery stenosis in two)	19.4±9.0
	Zhong, 2021 (31)	10	All male, 44.3±10.5	Arterial aneurysm (n=7), arterial stenosis (n=3), deep venous thrombosis of the lower limbs (n=2). Two patients had cardiac involvement (aortic valve lesion)	No	**CR** in 6, **PR** in 3, 1 relapse. (radiologic improvement of arterial lesions in 4)	6

M: male; F: female; CME: cystoid macular oedema; VA: visual acuity; IFX: infliximab; ADA: adalimumab; ETN: etanercept; GLM: golimumab; CR: complete remission; PR: partial remission; IQR: interquartile range.

amelioration of visual acuity in some cases. Attenuation of other BD clinical symptoms, such as mucocutaneous manifestations, with improvement of the BDCAF score was also observed in many patients (15). Similarly, TCZ improved neurologic manifestations in all patients with neuro-BD, except of one who had an infusion reaction and therefore the therapeutic effect if IL-6 inhibition could not be evaluated, and of another patient with haemorrhagic stroke, whose course was stable (29). In many cases, apart from clinical symptoms, MRI imaging findings improved after TCZ.

Regarding other BD clinical manifestations, TCZ induced complete remission in one patient with arterial stenosis with radiological improvement, as well as partial remission in a patient with intestinal BD with amelioration of her clinical condition and endoscopic images (23, 26). Finally, TCZ's effect on mucocutaneous symptoms was diverse, as from the 6 reported patients, only three responded to TCZ therapy. One patient with pemphigus foliaceus and oral and genital ulcers, erythema nodosum, uveitis, fever and arthralgias due to BD had a rapid (within 5 days) improvement of mucocutaneous symptoms and achieved complete and sustained remission (35). Another patient presented with mucocutaneous, joint and abdominal involvement and had complete resolution of mucosal and skin manifestations, while moderately severe arthralgias persisted. The third patient from our centre received TCZ for pyoderma gangrenosum and had complete remission, along with amelioration of neurological symptoms due to BD (18). The remaining three patients had a paradoxical exacerbation of mucocutaneous symptoms quickly after TCZ initiation that required discontinuation of treatment, even if in one of them there was a remarkable reduction of inflammatory markers. (34, 36) Similarly, one patient that received TCZ for severe arthralgias and acute confusional state without any mucocutaneous lesions, experienced an occurrence of major oral ulcers, that resolved spontaneously after TCZ discontinuation (19).

Safety

Overall, TCZ was well tolerated in the majority of patients and no new safety issues, other than those reported for other diseases, derived. Overall, there were 9 of 76 patients who experienced adverse events, including increases of cholesterol levels in two patients, mild respiratory tract infection, drop of leukocytes and neutrophils, recurrent urinary tract infection and recurrent labial herpes in one patient each. Two patients had to discontinue TCZ due to scrotal abscess and infusion reaction, respectively, whereas in one additional patient TCZ was temporarily withdrawn due to cellulitis with sepsis.

Discussion

Collectively, clinical observations summarised herein indicate that IL-6 inhibition is a legitimate therapeutic option for BD patients with refractory ocular, CNS and vascular involvement. However, only one prospective study has been published so far, focusing on refractory arterial involvement in BD, whereas there are no controlled trials. Most information comes from case reports and case series, therefore the actual benefit of TCZ in BD could be overestimated. TCZ has been reported effective for specific BD manifestations, such as BD uveitis and neuro-BD, that require prompt and aggressive initial therapy in order to control inflammation and prevent irreversible damage.

More specifically, TCZ was able to reduce or suppress ocular inflammation in 29 of 35 reported patients (one of whom relapsed and had to change treatment) and induce remission in 17 of 19 patients with neuro-BD, with amelioration of visual acuity or MRI imaging,

respectively, in many cases. (Table III) Similar results are reported on vascular involvement, as 15 of 17 patients, including 10 from a prospective study, achieved partial or complete response with radiographic improvement and steroid-sparing effect. (Table III) (26, 31). In another study, however, where TCZ was administered predominantly for ocular and CNS involvement, with remission in 13/16 and 3/5 respectively, articular manifestations improved in 4/7 patients, with complete remission of arthritis in two (29). Similarly, in a case series with 4 patients with BD uveitis, all had persisting arthralgias, despite remission of ocular involvement, and in another patient, that received TCZ for severe arthralgias and had to discontinue therapy due to occurrence of major oral ulcers, arthralgias persisted (18, 19).

Reports on the effects of TCZ on mucocutaneous lesions are also contradictory. Shapiro et al. were the first to report recurrence of oral ulcers in a patient with neuro-BD treated with TCZ, who otherwise had a complete remission of neurological involvement (16). Since then, there have been many reports of worsening of orogenital ulcers and skin lesions, even within days after the first infusion, requiring discontinuation of TCZ treatment (17, 19, 34, 36). In other cases, TCZ, while induced remission of BD uveitis or neuro-BD, had a minimum effect on oral ulcers. (29) On the other hand, there are reports of complete remission of mucocutaneous manifestations, even in cases that TCZ where was administered predominantly for other reasons (15, 31). Providing that these results will be confirmed, such discrepancies could be partly explained by the presence of different BD phenotypes based on the principal BD manifestation, *i.e.*, the mucocutaneous and articular phenotype, the extra-parenchymal neurological and peripheral vascular phenotype and the parenchymal neurological and ocular phenotype, that may have diverse therapeutic response and prognosis (40, 41). Another possible explanation is based on the fact that IL-6 may have an essential role in the wound healing process, as suggested by the delayed wound closure after IL-6 inhibition in mice, as well as by the development of chronic wounds in patients with dysregulation of IL-6 homeostasis (42, 43).

TCZ was also able to induce remission in two cases of renal AA amyloidosis, which, although rare, is the most common cause of renal disease and renal failure in BD.TCZ was able to decrease proteinuria after only the 2nd infusion and maintain serum creatinine levels (25, 33). The beneficial effect of TCZ on BD AA amyloidosis could be due to the fact that IL-6 is implicated in the pathogenesis of both BD and AA amyloidosis, as it stimulates SAA synthesis in hepatocytes and therefore promotes AA amyloidosis development. Therefore, IL-6 inhibition can reduce both inflammation and production of serum amyloid A protein (44, 45).

Interestingly, TCZ was effective in all but four anti-TNF naive patients (87%), two of whom initially responded but soon relapsed. Regarding anti-TNF experienced patients, TCZ was able to induce remission 80% of reported patients. In the majority of these patients, a significant reduction – and even withdrawal- of concomitant corticosteroid dose could be achieved (Tables I, II and III) (24, 26-28, 30, 31). TCZ was effective in patients that had previously been successfully treated with one or more anti-TNF agents and either lost efficacy or discontinued due to other reasons, as well as in patients previously unresponsive to anti-TNF drugs (37). On the other hand, there were few reports of no response to TCZ therapy in patients that had previously responded to TNF inhibitors, whereas re-initiation of an anti-TNF agent brought the disease under control. Especially regarding ocular involvement, a recent retrospective study by Leclercq *et al*. that compared the efficacy of anti-TNF agents vs TCZ for refractory uveitic macular oedema, concluded that TCZ was independently associated with complete response compared with anti-TNF agents after 6 months of treatment, which further suggests that IL-6 inhibition is a promising therapeutic option for inflammatory uveitis (32). However, from the 3 included patients with BD, only one had a complete remission of symptoms, one had a partial remission but relapsed and one had no response.

TCZ was administered intravenously either as monotherapy (or combined with corticosteroids alone) or, more often, in combination with other immunosuppressants, such as colchicine, azathioprine, methotrexate, cyclosporine or cyclophosphamide, for steroid-sparing reasons or to enhance efficacy. Remission was achieved in both cases, therefore the question as to whether TCZ should be used alone or combined with other csDMARDs remains open. Although evidence suggests that TCZ alone could suffice even in patients with severe forms of BD, comparative prospective studies are needed in order to address this issue. Moreover, TCZ was administered intravenously once a month in all patients, except of three to whom it was administered subcutaneously every week. Notably, in a patient with neuro-BD who had some loss of efficacy after a few months of TCZ treatment, reduction of intervals between intravenous infusions was capable to maintain disease control (38). Similarly, infusion intervals could be extended in a case where the disease was under control, with maintenance of remission (26).

Finally, there were no new safety issues emerging from TCZ treatment in BD, other than those already known from the use of TCZ in other rheumatic diseases.

To conclude, TCZ may be an alternative effective and safe therapeutic option for patients with BD, especially with ocular or CNS involvement requiring rapid disease control. However, TCZ's efficacy on BD mucocutaneous and articular phenotype may vary. Prospective controlled studies regarding the effect of TCZ on various BD manifestations are clearly needed to confirm these encouraging preliminary observations.

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