Tocilizumab may not be a good option for vascular involvement due to Behçet's syndrome

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Abstract

Objective

Tocilizumab has been increasingly reported as an alternative therapeutic agent in the management of Behçet's syndrome (BS) and it has been mostly tried in BS patients with neurological and eye involvement. As therapeutic responses to each drug may vary across different types of BS involvement, we aimed to report seven patients with large vessel involvement treated with tocilizumab.

Methods

We enrolled seven BS patients with vascular involvement who were given tocilizumab at the Behçet's Disease Research Centre in Istanbul University-Cerrahpaşa between 2000 and 2022. Demographic information, BS features, types of vascular involvement, previous and concomitant medications, C-reactive protein (CRP) levels, imaging modality results, and outcomes were documented from the patients' medical records.

Results

Within a median of 6 months after the initiation of tocilizumab, 5 patients experienced vascular relapses. These relapses included the emergence of new bilateral pulmonary artery aneurysms, a new pulmonary artery thrombus, parenchymal lung involvement, deep vein thrombosis in the lower extremity, and pseudotumor cerebri in one patient each. CRP levels were normal in 4 of the 5 patients at the time of vascular relapse. One of these 5 patients and another patient with aortitis had an exacerbation of mucocutaneous symptoms. In the last patient, venous ulcers did not respond to tocilizumab and were complicated with infection.

Conclusion

Tocilizumab could potentially exacerbate vascular manifestations, similar to what is observed with mucocutaneous lesions in BS patients. Furthermore, CRP levels appear to be ineffective in monitoring these patients.

Key words

Behçet's syndrome, tocilizumab, vascular involvement, pulmonary artery aneurysms, deep vein thrombosis

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Introduction

Behçet's syndrome (BS) is a complex multisystemic inflammatory disease of unknown aetiology (1). Recurrent oral and genital ulcers, skin lesions and sight threatening uveitis are the hallmark manifestations of the disease (1). Locomotor, vascular, central nervous and gastrointestinal systems may also be involved. Vascular involvement in BS is characterised with recurrent venous thrombosis. Arterial involvement is less common and manifested with aneurysm formation rather than thrombotic occlusions (2). Vascular involvement may be observed in up to 40% of BS patients, with frequency varying across regions, and is associated with severe morbidity and increased mortality.

The management of major organ involvement including vascular manifestations in BS patients involves the use of glucocorticoids along with immunosuppressive agents (3-4). Monoclonal anti-tumour necrosis factor (TNF)-alpha antibodies are the most commonly prescribed biologic agents for BS, and they have demonstrated efficacy for all types of involvement in BS, even in cases of refractory or relapsing disease. However, some patients may not achieve remission, or fail to maintain remission over time with monoclonal anti-TNF antibodies, necessitating exploration of alternative targeted biologic options.

Tocilizumab targets the interleukin-6 (IL-6) receptor and is effective in various inflammatory conditions, such as rheumatoid arthritis, giant cell arteritis, and systemic sclerosis (5-6). It has also been proposed as an alternative therapeutic option for BS patients after the initial studies suggested a crucial role for IL-6 in the pathogenesis of parenchymal neurological involvement (7). Among the approximately 130 reported BS patients in the PubMed (8-11), tocilizumab has been mostly tried in the management of neurological and ocular involvement in BS showing promising results. However, there are also cases where tocilizumab may be associated with exacerbations of mucocutaneous manifestations (12-14). Limited data are available regarding its use in vascular involvement in BS (15-16). Two observational studies from China, including a total of 17 patients, showed that tocilizumab may be considered as an option for refractory non-pulmonary arterial involvement (15-16).

In this case series, we report 7 BS patients with vascular involvement who were treated with tocilizumab, resulting in unfavourable outcome.

Material and methods

We included seven patients who received tocilizumab and followed in the Behçet's Disease Research Centre in Istanbul University-Cerrahpaşa between 2000 and 2022. All patients fulfilled the diagnostic criteria for BS (17). Demographic data, BS manifestations, disease duration, type of vascular involvement, previous drugs, C-reactive protein (CRP) levels, the route and dose of tocilizumab administration, results of imaging modalities, and outcome were recorded from the patients' medical charts.

The study protocol was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty (83045809-604.01.01-898059/06/02/2024). Informed consent was obtained from the patients. All study procedures were carried out in accordance with the ethical standards of the Helsinki Declaration.

Results

Table I presents the demographic and clinical findings, as well as the medications of the patients, and Table II provides details on tocilizumab administration and outcomes.

Among the 7 patients included in this case series, all fulfilled International Study Group criteria (17), and 4 were male. The median disease duration and age at tocilizumab initiation were 20 years (IQR: 11) and 47 years (IQR: 10), respectively. As shown in Table I, all patients, except for one, had multiple vascular lesions, such as: lower extremity deep vein thrombosis (DVT) (n=4), pulmonary artery involvement (n=3), cerebral venous sinus thrombosis (CVST) (n=3), intracardiac thrombosis (n=2), vena cava inferior thrombosis (n=1), carotid artery aneurysm (n=1), aortitis (n=1), venous ul-

Table I. Demographic and clinical findings of the patients and the medication details prior tocilizumab.

Case no.	Age/sex	BS features	Disease duration	Cardiovascular lesions	Indication for tocilizumab	Outcome
1	28/M	OU, GU, PP, EN	18 years	Pulmonary artery thrombosis, intracardiac thrombosis, cerebral venous sinus thrombosis, vena cava inferior thrombosis, lower extremity deep vein thrombosis	Fever and high acute phase reactants	Bilateral pulmonary artery aneurysms appeared
2	46/M	OU, GU, PP	20 years	Lower extremity deep vein thrombosis, pulmonary artery thrombosis, intracardiac thrombosis	Constitutional symptoms and high acute phase reactants	A new right pulmonary artery thrombosis developed.
3	48/F	OU, GU, PP, J	22 years	Pulmonary artery aneurysm and thrombosis	Arthritis and high acute phase reactants	In addition to worsening of mucocutaneous lesions, parenchymal lung involvement developed.
4	49/F	OU, GU, EN, J	29 years	Cerebral venous sinus thrombosis, lower extremity deep vein thrombosis, vena cava inferior thrombosis	AA amyloidosis and high acute phase reactants	Deep vein thrombosis in the left lower extremity developed.
5	47/M	OU, GU, PP, EN	20 years	Lower extremity deep vein thrombosis, venous ulcer, bilateral carotid artery aneurysms	Venous ulcer and high acute phase reactants	In addition to no healing of the venous ulcer, ulcers were complicated with infection.
6	39/M	OU, PP, EN, J, U	14 years	Cerebral venous sinus thrombosis and superficial thrombophlebitis	Arthritis, nodular lesions, and high acute phase reactants	A relapse of cerebral venous sinus thrombosis developed.
7	68/F	OU, GU, PP, GIS	35 years	Aortitis and pericarditis	Aortitis, pericarditis, and high acute phase reactants	Mucocutaneous symptoms were exacerbated, however, aortitis responded to tocilizumab well.

EN: erythema nodosum like lesions; GIS: gastrointestinal system involvement; GU: genital ulcer; J: joint involvement; OU: oral ulcers; PP: papulo-pustular lesions; U: uveitis.

Table II. Previous medications before tocilizumab and details associated with tocilizumab use.

Case no.	Medications before tocilizumab	Medications just before tocilizumab	Tocilizumab administration	Concomitant medications	Duration of tocilizumab treatment
1	Azathioprine, cyclophosphamide, infliximab, adalimumab, etanercept, prednisolone	Adalimumab 40 mg/every week SC	162 mg/week SC	Azathioprine Prednisolone	6 months
2	Azathioprine, cyclophosphamide, interferon-alpha-2b, infliximab, adalimumab, canakinumab, prednisolone	Adalimumab 40 mg/every other week SC	8mg/kg/every 4 weeks IV	Prednisolone	5 months
3	Cyclophosphamide, interferon-alpha-2b, infliximab, prednisolone	Infliximab 5mg/kg IV	162 mg/week SC	Colchicine Prednisolone	6 months
4	Azathioprine, interferon-alpha-2b, anakinra, prednisolone	Anakinra 100 mg/day SC	8mg/kg/every 4 weeks IV	Azathioprine Prednisolone	3 months
5	Azathioprine, cyclophosphamide, interferon-alpha-2b, infliximab, prednisolone	Pegylated interferon-alpha-2a 135 mg/week SC	162 mg/week SC	Prednisolone	12 months
6	Infliximab, adalimumab, interferon-alpha-2b, interferon-alpha-2a pegylated interferon-alpha-2a, prednisolone	Adalimumab 40 mg/every week SC	162 mg/week SC	Prednisolone	4 months
7	Azathioprine, cyclophosphamide infliximab, prednisolone	Infliximab 5 mg/kg IV	162 mg/week SC	Colchicine	18 months

SC: subcutaneously; IV: intravenously.

cer (n=1), superficial thrombophlebitis (n=1), and pericarditis (n=1). In addition to vascular involvement, 3 patients had another type of major organ involvement (eye involvement: n=2 and gastrointestinal involvement: n=1).

All patients had previously received conventional and at least one biologic immunosuppressive agent before tocilizumab administration (Table II). The primary indications for tocilizumab initiation were both constitutional symptoms and elevated acute phase reactants in 2 patients, persistent high acute phase and joint involvement in 1 patient, both joint involvement and recurrent superficial thrombophlebitis in 1, both aortitis and pericarditis in 1, venous ulcer in 1, and AA amyloidosis in 1. While 5 patients were initiated tocilizumab with a dose of 162 mg/week subcutaneous therapy, 2 patients received it with monthly infusion therapy at a dosage of 8 mg/kg.

Overall, within a median of 6 months after tocilizumab initiation, 5 patients experienced a vascular relapse, of whom one developed mucocutaneous lesion, 1 patient developed cellulitis and lymphedema on the leg with ve-

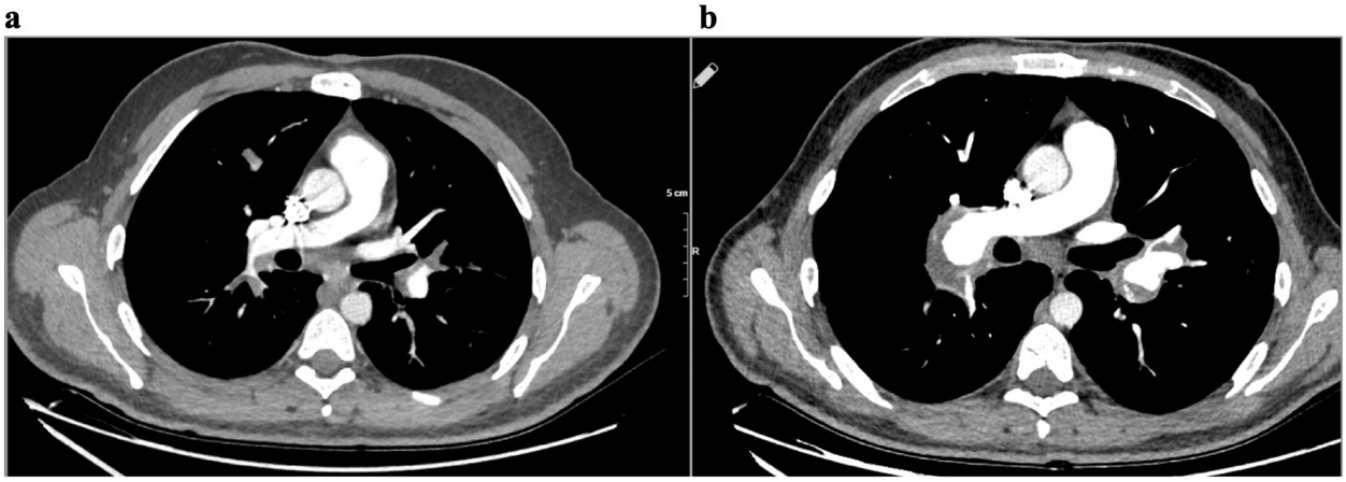

Fig. 1. Thorax computed tomography (CT) images of Case 1 before (**a**) and after (**b**) tocilizumab therapy.
a) Axial contrast-enhanced CT scan shows thrombosis at the right lower and left upper and lower pulmonary arteries before tocilizumab treatment.
b) Axial contrast-enhanced CT scan shows bilateral giant saccular partially thrombosed pulmonary artery aneurysms after tocilizumab treatment.

nous ulcer, and the remaining patient with aortitis had an exacerbation of mucocutaneous lesions. All patients had elevated CRP levels at tocilizumab initiation, and these levels returned to normal within 2-5 weeks after tocilizumab initiation in 6 patients. However, in one patient (Case 6), acute phase response persisted. Among the five patients who had a vascular relapse, except one (Case 6), CRP levels were within normal limits at the time of vascular relapse. By the time study follow-up ended, one patient was still using tocilizumab for 18 months and in this patient aortitis responded well to tocilizumab.

Case series

Case 1. A 28-year-old male patient had recurrent oral aphthous ulcers and papulo-pustular lesions since his teenage years. Throughout 4-year follow-up from his first presentation in 2017 until 2021, he developed pulmonary artery thrombosis, intra-cardiac thrombosis, inferior vena cava thrombosis, Budd-Chiari syndrome, bilateral DVT on the lower extremities, CVST and jugular vein thrombosis, despite receiving intensive treatment with cyclophosphamide courses, interferon-alpha-2b and anti-TNF agent (infliximab, adalimumab and etanercept) along with high doses of glucocorticoids. All these vascular events were accompanied with bouts of fever and elevation in the acute phase response. In November 2021, while he was receiving etanercept 50 mg/weekly he presented with fever, constitutional symptoms and high CRP levels. Imaging modalities did not reveal any new vascular involvement. Tocilizumab 162 mg per week was initiated, resulting in the prompt resolution of his symptoms and acute phase elevation. However, in the fifth month of tocilizumab treatment, he presented with dyspnoea, haemoptysis, and dry cough. Thorax CT angiography detected bilateral large pulmonary artery aneurysms with the largest diameter measuring 3.5 cm (Fig. 1). Tocilizumab was stopped and 1 g intravenous cyclophosphamide along with high dose glucocorticoids was started, followed by oral 150 mg/day cyclophosphamide and certolizumab 200 mg every other week.

Case 2. A 46-year-old male patient was diagnosed with BS in 2002 based on recurrent oral aphthous ulcers, genital ulcers, and eye involvement. In 2006, he developed DVT on the right lower extremity and PAT while receiving azathioprine. He received initially cyclophosphamide, followed by infliximab monotherapy as maintenance for 8 years through 2006-2014, during which he did not experience any thrombotic attack. In 2014, following an infusion reaction, infliximab was switched to first interferon-alpha-2b then to canakinumab, which both turned out to be unsuccessful. Finally, adalimumab 40 mg every other week maintained him in remission between 2015 and 2022. In January 2022, he was hospitalized with severe chills and fever attacks, weight loss and elevated CRP levels of 6 weeks duration. Imaging modalities did not reveal new or active vascular involvement, and tocilizumab 8mg/kg was started. In the fifth month of tocilizumab treatment, he presented with progressive exertional dyspnoea and haemoptysis despite having normal CRP levels. Thorax CT angiography revealed new thrombus formations in the pulmonary arteries (Fig. 2). Tocilizumab was stopped. After 4 doses of 1 g intravenous monthly cyclophosphamide along with high dose glucocorticoids, certolizumab 200 mg every other week was initiated.

Case 3. A 48-year-old female patient had BS for 22 years (2000). She had been diagnosed with pulmonary artery aneurysms 5 years after BS onset (2005). She had been remission since 2008. After cyclophosphamide induction treatment, she was followed with azathioprine monotherapy as maintenance for 10 years. Azathioprine was stopped due to leukopenia in 2018 and infliximab 5 mg/kg was started which she received until 2022. Because of persisting high acute phase response and recurrent knee arthritis under infliximab, she was switched to tocilizumab 162 mg per week. Four months later she presented with a large oral ulcer, a lesion which she had not experienced for the last 20 years, and arthritis on

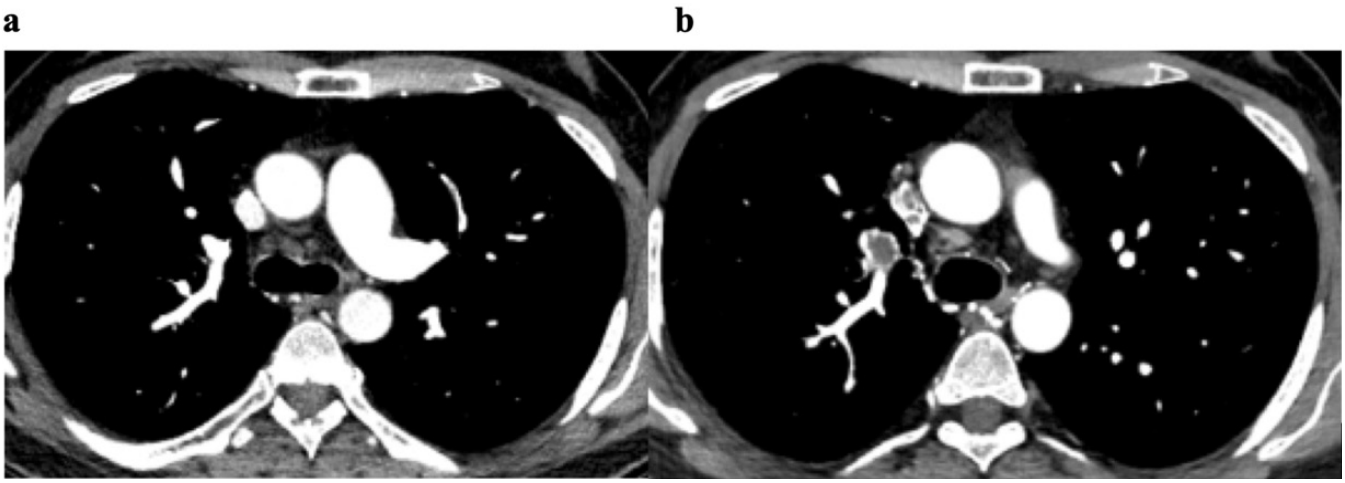

Fig. 2. Thorax computed tomography (CT) images of Case 2 before (**a**) and after (**b**) tocilizumab therapy.
a) Axial contrast-enhanced CT scan shows normal right upper lobe pulmonary artery. **b**) Axial contrast-enhanced CT scan shows saccular thrombosed aneurysm at the right upper lobe pulmonary artery.

the knee that required intra-articular steroid injection. Nevertheless, she continued tocilizumab treatment. Then three weeks later, she presented with haemoptysis, a symptom that she had not experienced since 2005. Thorax CT angiography revealed ground glass opacities in the parenchyma which was attributed to BS parenchymal involvement. Tocilizumab was discontinued, and certolizumab 200 mg every other week was started in addition to high-dose glucocorticoids.

Case 4. A 49-year-old female patient was diagnosed with BS in 1993 with recurrent oral aphthous ulcers, genital ulcers, erythema nodosum and left knee arthritis. In 2006, she presented with CVST and DVT on the lower extremities. Between 2006 and 2020, she received treatment involving azathioprine and glucocorticoids, but there were multiple interruptions in the management due to issues with adherence. She presented with pleural effusion, pericardial effusion, proteinuria, and ascites in 2020. A renal biopsy confirmed AA amyloidosis. First anakinra 100 mg subcutaneously per day was initiated due to the progression of proteinuria. Her creatinine level and proteinuria progressed despite using anakinra, and she developed chylous ascites. Peritoneal biopsy also revealed AA amyloidosis. Tocilizumab 8mg/kg was started. However, at the third month of tocilizumab treatment, she started to have recurrent attacks of DVT on the left lower extremity. Tocilizumab was stopped and anakinra 200 mg/day was reinstituted.

Case 5. This was a 47-year-old male patient had been diagnosed with BS in 2002. Three years after BS diagnosis, he developed DVT on the lower extremities and bilateral carotid artery aneurysms. Carotid aneurysms were managed without surgery with only cyclophosphamide for 3 years and exhibited significant regression during the course. However, the patient, developed venous ulcers in his lower extremities which were refractory to azathioprine and infliximab combination as well as subcutaneous injections of interferon alpha-2a and pegylated interferon alpha-2a. Due to the persistence of venous ulcers and high acute phase reactants, he was switched to tocilizumab. Despite prompt decrease in the acute phase response, number of ulcers and their dimensions remained stable. Nevertheless, the patient continued to receive tocilizumab treatment for 12 months. Tocilizumab was stopped following an acute onset of cellulitis and lymphedema on the leg which had the most prominent ulcers. While blood and tissue cultures were sterile, he recovered with antibiotics alone.

Case 6. A 39-year-old male patient was diagnosed with BS in 2008 due to recurrent oral aphthous ulcers, papulopustular lesions, arthritis, uveitis, and CVST. Because of refractory course characterised with recurrent attacks accompanied by high acute phase response, he used several immunosuppressives including azathioprine, interferon-alpha-2b, pegylated interferon-alpha-2a and monoclonal anti-TNF agents (infliximab and adalimumab). In 2022, adalimumab dose was intensified to 40 mg every week for 3 months due to ongoing acute phase elevation, arthritis, and erythema nodosum. However, this regime also resulted in inefficacy. Tocilizumab 162 mg per week was initiated. In the fourth month of tocilizumab, he experienced severe headache and hearing deficit, which were attributed to pseudotumor cerebri, although cranial MR did not show a new thrombosis on the sinuses. Tocilizumab was stopped, and certolizumab 200 mg was started along with high dose glucocorticoids.

Case 7. A 68-year-old female patient was diagnosed with BS in 1988 due to recurrent oral aphthous ulcers and genital ulcers. She received colchicine for a short time. In 1994, she presented with haematochezia, abdominal pain and diarrhoea, a large ulcer in the terminal ileum was detected on colonoscopy. She was treated with azathioprine and glucocorticoids. Between 1996 and 2018, pretending being in remission, she did not show up her regular outpatient appointments and did not

Table III. Literature review tocilizumab outcomes on vascular lesions in BS patients.

Study	N (M/F)	Age, median (IQR)	Clinical features	Vascular lesions	Concomitant Treatment	Prior treatment	Duration of follow up median (IQR), months	Outcome	Adverse event
Ding, 2018 (15)	7, M/F: 6/1	30, (IQR:19)	OU (n=7), GU (n=5), S (n=6), GIS (n=1), J (n=2), U (n=1), P (n=3)	Arterial aneurysm (n=5) Arterial stenosis (n=4) Arterial occlusion (n=3) AAA (n=4), AOAR (n=3), CA (n=2), CCA (n=4), FA (n=2) VI (n=1)	Prednisone (n=7) CYC (n=7), AZA (n=5), LEF (n=2) MTX (n=2) ETN (n=1) TAC (n=1)	Prednisone (n=7), CYC (n=4), AZA (n=5), LEF (n=1) MTX(n=1)	20 (IQR:11)	Complete remission (n=4), Partial remission (n=3)	
Zhong, 2022 (16)	10, M/F:10/0 All male	48.5, (IQR: 28)	OU (n=10) GU (n=4), S (n=8), GIS (n=1), J (n=2), U (n=1), P (n=5)	Arterial aneurysm (n=7) Arterial stenosis (n=3) AAA (n=2), TAA (n=2), AA (n=1), IA (n=1), CCA (n=1), VI (n=1), AV (n=2) CA (n=4)	Prednisone (n=10) CYC (n=4), MMF (n=3) AZA (n=2), TAC (n=1)	Prednisone (n=10), CYC (n=7), MMF (n=3), TAC (n=1), AZA (n=2)	22.5 (IQR:20)	Complete remission (n=5), Partial remission (n=4), **Enlargement in abdominal aortic aneurysm (n=1)**	Mild respiratory tract infection (n=1)

GIS: gastrointestinal system involvement; GU: genital ulcer; J: joint involvement; OU: Oral ulcers; P: Pathergy positivity, S: skin lesions; U: uveitis; CYC: cyclophosphamide; ETN: etanercept; MTX: methotrexate; MMF: mycophenolate mofetil; TAC: tacrolimus; AZA: azathioprine; AA: ascending aorta; AAA: abdominal aortic aneurysm; TAA: thoracoabdominal aneurysm; AOAR: aortic arch; AV: aortic valve; CCA: common carotid artery aneurysm; FA: femoral artery; IA: iliac artery aneurysm; VI: visceral artery stenosis; CA: coronary artery.

receive any medication. In 2018, she presented with constitutional symptoms, acute phase elevation, and pericarditis. Positron emission tomography revealed aortitis in the thoracic aorta, she received 6 doses of intravenous cyclophosphamide, along with high dose glucocorticoids. This was followed by infliximab 5 mg/kg monotherapy however, due to an allergic reaction, tocilizumab 162 mg per week was started. After that, she began to suffer from recurrent oral and genital ulcers, although symptoms associated with pericarditis improved and her acute phase response has decreased considerably. Colchicine was added and tocilizumab intervals were prolonged to 15 days. By the time the manuscript was written, she was still on tocilizumab for 18 months, and the treatment interval was extended to every 6 weeks.

Discussion

Our small case series revealed rather important observations. Seven patients with previous vascular involvement due to BS were treated with tocilizumab because of high acute phase response for a median of 6 months. Acute phase response decreased right after receiving the drug in all except one, however, five flared with severe vascular involvement and one remained stable. A positive response was noted only in the patient with aortitis. However, this improvement was accompanied by exacerbation of skin-mucosa ulcerations.

Vascular events that occurred post-tocilizumab were *de novo* occurrence of bilateral pulmonary artery aneurysms, new thrombotic formations in the pulmonary arteries, parenchymal lung involvement, DVT in the lower extremity, and pseudotumor cerebri. It has to be noted that, although patients had long history with refractory vascular disease, the main reason for tocilizumab initiation was high acute phase response and many of them did not experience such a severe main vascular event for years prior to tocilizumab use. Therefore, our data at hand, together with the reappearance of skin mucosa lesions after almost a decade later in two patients indicate that tocilizumab quite possibly is responsible for the induction of these vascular events. Another important point to consider is that CRP levels were within the normal range in four out of the five patients who had a vascular relapse. This suggests that systemic inflammation which could be potentially reducible with anti-IL 6 and vascular inflammation seem to be driven by distinct disease mechanisms in BS. This is similar to what have been postulated for Takayasu's arteritis (18). Our observation could also have clinical implications, suggesting that the utility of acute phase reactants in guiding therapy for BS may be diminished in patients using tocilizumab. Therefore, there is no other parameter left other than clinical findings and radiological examinations.

We did a review of the literature published in English on PubMed until March 11, 2024, using the keywords 'Behçet' and 'tocilizumab'. Among the 99 reported studies, two case series (15-16) identified tocilizumab use in vascular involvement due to BS; one included 7 patients and the other 10 (Table III). In total, 16 of the 17 patients were male, and their median ages were 30 (IQR:19) and 48.5 (IQR:28) respectively (15-16). The median duration of tocilizumab use in these case series was 20 months (IQR:11) and 22.5 months (IQR: 20), respectively. All patients had non-pulmonary arterial involvement manifested as aneurysms (n=12) with or without stenosis (n=6). Arterial involvement was identified in the abdominal aorta (n=6), aortic arch (n=4), aortic valve (n=2), carotid artery (n=5), thoracoabdominal aorta (n=2), coronary artery (n=6), iliac artery (n=1), femoral artery (n=2) and visceral artery (n=2). All were refractory to conventional DMARDs and only one had used etanercept as biological agent. Complete response was observed in 9/17 (53%), whereas partial response in 6/17 (35%), and in 1/17 enlargement of an

abdominal aortic aneurysm was reported. No outcome information was available in the remaining patient. It should be emphasised that these patients (15-16) exhibited aortic and branch involvement similar to that seen specifically in a large vessel vasculitis, rather than the typical venous thrombotic or pulmonary involvement attributed to BS.

In a systematic review (11) that included articles published until December 2021, tocilizumab has been reported to be a promising biologic agent (9-14). In this review (11), there were 74 patients, of whom 31 were anti-TNF naïve. The primary indications for tocilizumab initiation other than vascular involvement that we reviewed in detail in the previous paragraph, were uveitis (n=33), neurological involvement (n=15), mucocutaneous and/or joint involvement (n=7), AA amyloidosis (n=2), gastrointestinal involvement (n=1), and MAGIC syndrome (n=1). Complete and partial responses among patients with uveitis [17/35 (49%) and 12/35 (34%), respectively] and among those with neurological involvement [8/19 (42%) and 11/19 (58%), respectively] were reported. On the other hand, similar to our observation, five of the reported patients in this systematic review experienced a mucocutaneous flare with tocilizumab (11-14). After the release of this systematic review, three additional manuscripts were published reporting 42 BS patients who were treated with tocilizumab (8-10). In the first article, tocilizumab did not lead to remission in three BS patients with uveitis (8). The second study was a multicentre study including 30 BS patients who were intolerant or refractory to anti-TNF treatment (9). They received tocilizumab due to uveitis (n=18), neurological involvement (n=5) and mucocutaneous and/or joint involvement (n=7). Again, complete and partial responses at month 6 were reported [uveitis: 12/18 (67%) and 3/18 (17%); neurological involvement: in 3/5 and 2/5, and mucocutaneous and/or joint involvement: 3/7 and 2/7 (29%)] (9). In the third multicentre study (10), the authors compared the treatment outcomes of 49 patients with BS uveitis who were treated with infliximab (n=15), adalimumab (n=25), or tocilizumab (n=9). There were no significant differences regarding treatment response, remission, and adverse events between the study groups.

BS shows significant heterogeneity in clinical manifestations, and several studies have identified distinct clinical phenotypes in BS patients (2). The heterogeneity in the clinical spectrum extends to the response of medical therapies for each type of organ involvement. Different treatment responses to various manifestations are well-known in BS. Colchicine, the first-line treatment for mucocutaneous and joint involvement, is not effective for major organ involvement in BS. Thalidomide which is effective for skin-mucosa lesions, may exacerbate erythema nodosum-like lesions (19). Cyclosporine-A is the main treatment option for uveitis but is contraindicated in neuro-BS (20). Cyclophosphamide is not an option for uveitis whereas is the main drug for pulmonary artery aneurysms (21). Secukinumab has been suggested as an option for joint involvement in BS (22); however, it failed to meet its primary endpoint in BS uveitis in a randomised controlled study (23). Moreover, it was reported to exacerbate BS manifestations and may even induce the occurrence of *de novo* BS (24-28). Furthermore, treatment response of a drug may differ in the same BS patient for different organ involvement, as 7% of the patients using infliximab may experience *de novo* manifestations under infliximab despite achieving remission in involvement requiring infliximab (29).

Our study is clearly limited by its retrospective nature, small patient cohort, and not being randomised controlled study.

In conclusions, this case series, suggests that tocilizumab may not be an option for BS patients with vascular involvement. Tocilizumab may exacerbate vascular manifestations, as it does with mucocutaneous lesions among BS patients. Furthermore, caution is required as CRP levels appear to be useless in monitoring patients receiving this drug.

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