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Original article

Efficacy and safety of tocilizumab in Behçet's syndrome with refractory arterial lesions: a single-centre observational cohort study in China

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Abstract

Objective. The aim of this observational cohort study was to assess the effectiveness and safety of the IL-6-receptor inhibitor tocilizumab (TCZ) in Behçet's syndrome (BS) with refractory arterial involvement.

Methods. Ten patients admitted to the Rheumatology and Immunology Department of Peking University People's Hospital between January 2014 and December 2019 were enrolled. The enrolled patients met the BS international criteria and exhibited severe arterial impairments. Refractory arterio-BS was diagnosed based on objective vascular symptoms unexplainable by other known illnesses, and resistance to traditional immunosuppressants and glucocorticoids after 12 weeks. Patients received 8 mg/kg TCZ infusions every 4 weeks for $\geq$24 weeks, with simultaneous continuation of immunosuppressants and glucocorticoids. Clinical and imaging data were assessed before and after TCZ treatment.

Results. The enrolled patients were men aged 44.3 (10.5) years; the median disease duration was 186.5 (45.7) months, and the average age of arterial impairment onset was 38.7 (12.9) years. The following trends were observed: improvement and maintenance of symptoms after the 26.8 (7.2)-month follow-up, $n = 9$; complete remission, $n = 6$; partial response, $n = 3$; immunosuppressant dose reduction, $n = 4$; radiologic improvement of arterial lesions, $n = 4$; and TCZ discontinuation owing to enlarged abdominal aortic aneurysm relapse, $n = 1$. The average daily glucocorticoid dose reduced from 54.5 (20.6) to 8.3 (3.6) mg/d ($P < 0.001$), while the median ESR and CRP values reduced from 50 (2–82) mm/h and 32.9 (2.1–62.3) mg/dl to 4 (1–10) mm/h and 2.9 (0.2–12.1) mg/dl, respectively ($P < 0.001$). No TCZ-associated side effects were noted.

Conclusion. TCZ proved to be safe and effective for refractory arterial lesions in BS, with a steroid- and immunosuppressant-sparing benefit.

Key words: Behçet's syndrome, arterial involvement, tocilizumab, efficacy, real-life study

CLINICAL SCIENCE

Rheumatology key messages

- Arterial lesions present a clinical challenge for treating Behçet's syndrome.
- Tocilizumab may be safe and effective for refractory arterial lesions in Behçet's syndrome.

Introduction

Behçet's syndrome (BS) is a chronic and relapsing vasculitis that includes recurrent oral aphthous ulcers, along with genital ulcerations, skin lesions, and uveitis. Patients may also present arthralgia, venous and arterial thrombosis, and neurological involvement [1]. In BS, major vascular disease is a leading cause of death and morbidity [2]. Classic immunosuppressants constitute most of the therapeutic arsenal, which includes cyclophosphamide (CYC), mycophenolate mofetil (MMF), tacrolimus (TAC), cyclosporin (CSA), azathioprine (AZA), and, more recently, anti-tumor necrosis factor (TNF)-α medications [3]. However, no substitute therapeutic

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strategy has been indicated in cases of resistance to these therapies [4].

Several investigations have found circulating IL-6 levels to be elevated in BS patients, correlating with disease activity [5–8]. Tocilizumab (TCZ) may suppress IL-6 action, suggesting that it could be a useful therapeutic target for refractory BS [9, 10]. TCZ is a completely humanized monoclonal antibody, demonstrated to be efficacious in patients with refractory ocular involvement [11–13]; however, studies evaluating TCZ efficacy in arterial involvement of BS are scarce.

This single-centre, real-world study aimed to assess the safety and effectiveness of TCZ therapy in 10 patients with BS and severe arterial involvement.

Methods

The study was approved by the Institutional Medical Ethics Review Board of Peking University People's Hospital (2021PHB139-001) and conducted in compliance with the Declaration of Helsinki. On enrolment, all patients signed a written informed consent form.

Patients

This study enrolled 10 patients aged >18 years; all patients had major arterial involvement that was treated with standard immunosuppressants, and satisfied the international criteria for BS. The presence of an arterial or cardiac valvular lesion was used to identify major arterial involvement. Angio-BS was diagnosed based on objective vascular symptoms that were not explained by any other known illness, as well as imaging results suggestive of BS-related vascular involvement. All patients had received appropriate immunosuppressant (IS) therapy, which included CYC ($n = 7$), MMF ($n = 2$), AZA ($n = 2$), TAC ($n = 1$), and high doses of CSs (prednisone ≥1 mg/kg/d).

Patients were regarded as being resistant to traditional therapy if they exhibited a poor clinical response and elevated serum inflammatory markers as their condition progressed. Patients were considered as being intolerant to traditional therapy if they had any steroid-related contraindications (e.g. diabetes, hypertension, or osteoporosis), or at least one adverse event (AE) associated with the use of additional immunosuppressants (e.g. hypocytosis, gastrointestinal response, 3-fold increase in liver enzymes, serum creatinine >1.5 mg/dl, or 30% decrease in glomerular filtration rate). The duration of conventional immunosuppressives before identifying the patient as refractory was at least 3 months. Patients 1, 2, 3, 5, 6, 7 and 9 were switched to TCZ because they were refractory, while patients 4, 8 and 10 were intolerant to previous immunosuppressives. Ten patients were administered TCZ infusions once every 4 weeks (8 mg/kg per dose). Concomitant immunosuppressive and glucocorticoid treatment was continued, with a gradual decrease in glucocorticoid dosage. All patients were prospectively followed-up for at least 24 weeks.

Data collection and outcome evaluation

All patients were followed for 24 weeks. Data regarding patient age and sex; diagnostic information and clinical features of BS; vascular imaging results; therapeutic approach, such as drug, dose and duration; and effectiveness were collected. We assessed each patient's clinical, biological and radiological response to TCZ, as well as the time to remission, disease recurrence, and side effects of TCZ.

Clinical and biological remissions of vascular lesions were detected using echocardiography, angio-CT and vascular Doppler sonography. Complete remission was defined as the resolution of initial symptoms and inflammatory parameters, absence of new vascular lesions in BS, and administration of a CS dose of <10 mg/day following TCZ therapy at 24 weeks. A partial response was described as an improvement in clinical manifestations and inflammatory indicators, along with a >50% decrease in the original glucocorticoid dose following TCZ therapy at 24 weeks. Relapse was characterized by the recurrence of symptoms and imaging vascular impairments, as well as the emergence of new BS-linked vascular lesions.

Changes in the Behçet's Syndrome Activity Score (BSAS), Behçet's Disease Current Activity Form (BDCAF) score, and the number of oral ulcers at week 24 were among the other study outcome measures. All patients were observed for AEs every 4 weeks until the end of the study and, for some patients, at the last available follow-up.

Statistical analysis

Normally distributed continuous data are displayed as means and S.D.s or medians. Counts and proportions or percentages were used to present categorical variables. The Shapiro–Wilk test was used to analyse the normal distribution assumption of the quantitative outcomes. For between-group comparisons, Student's *t* test and the Mann–Whitney *U* test were used for numerical variables, and the χ^2 test for categorical variables. All tests were two-sided, and statistical significance was set at $P < 0.05$. All data analyses were performed using SPSS 25.0.

Results

Main characteristics of the BS patients

Table 1 summarizes the characteristics of the 10 patients. This study enrolled 10 male BS patients with severe artery lesions, and an average age of 44.3 (10.5) years upon first diagnosis of BS; the mean age of initial appearance of vascular impairment was 38.7 (12.9) years. The median duration from disease onset to major arterial involvement was 11.0 (10.1) years. Together with high-dose CSs, conventional treatments were CYC, MMF, tacrolimus, and AZA in seven, three, one and two patients, respectively. Four patients

Table 1 Tocilizumab therapy in the 10 cases of refractory arterio-Behçet's syndrome

Patient	Sex/age, years	Age of arterial involvement, years	Disease duration, months	Clinical features[a]	Arterial lesions	Number of TCZ	Previous therapy	Concurrent treatment	Duration of follow-up, months	Response at week 24[b]	Surgery	The outcome of arterial imaging manifestations
1	Male/34	32	228	O, G, P, S, I	Stenosis of CA/SMA/RenA/SCA, aortic valve prolapses	8	Pred/CYC/MMF	Pred/MMF	25	CR	–	Severe aortic regurgitation reduced to moderate on echocardiogram, ejection factor raised from 53% to 66%; the diameter of the AA increased by 0.3 cm on CTA, and the degree of stenosis for the CA, SMA and RenAs had reduced.
2	Male/20	18	24	O, S	Dissecting aneurysm of AA (Debakey I)	7	Pred/MMF	Pred/MMF	24	PR	Prosthetic vessel replacement of aorta	Vascular US was normal after artificial blood vessel replacement surgery.
3	Male/67	54	276	O, G, P, S, A	Thoracoabdominal aortic aneurysm	6	Pred/CYC/TAC	Pred/TAC	8	CR	Thoracic artery stenting	A penetrating ulcer of the aortic arch was healing, while the diameter of the aneurysm grew from 5.5 cm × 3.7 cm to 7.0 cm × 5.4 cm.
4	Male/67	56	75	O, S, U	Stenosis of LAD/LCX/RCA	3	Pred/CYC	Pred/CYC	7	CR	–	Scattered ulcers on aortic arch and distal segments of the abdominal aorta were healing on CTA.
5	Male/50	43	80	O, G, A	Abdominal and coronary aortic aneurysms	7	Pred/CYC	Pred/CYC	21	Relapse	Abdominal artery stenting	Diameter of aneurysm on right coronary artery reduced from 3.8 cm × 2.8 cm to 1.8 cm × 2.5 cm, while the diameter of the aneurysm on abdominal aorta increased from 4.9 cm × 3.1 cm to 6.3 cm × 4.5 cm.
6	Male/48	46	26	O, G	Aortic insufficiency	6	Pred/CYC	Pred/CYC	15	PR	–	Severe aortic regurgitation reduced to moderate on echocardiogram.
7	Male/26	24	147	O, P, S, V	Iliac artery aneurysm	7	Pred/MMF	Pred/MMF	16	CR	–	Partial recanalization of right lower extremity deep vein (based on vascular US), while iliac artery aneurysm remained the same size.
8	Male/49	41	466	O, S, V	Thoracoabdominal and coronary aortic aneurysms	24	Pred/CYC/AZA	Pred/AZA	72	CR	Abdominal artery stenting	The diameter of the aneurysm on the coronary artery reduced from 3.8 cm × 2.7 cm to 1.4 cm × 1.1 cm on cardiac MRI.
9	Male/27	23	181	O, P, S	Pseudoaneurysm of CCA	6	Pred/CYC	Pred/CYC	45	PR	–	Diameter of left CCA pseudoaneurysm reduced from 4.3 cm × 3.7 cm to 3.2 cm × 3.1 cm on CTA.

(continued)

TABLE 1 Continued

Patient	Sex/age, years	Age of arterial involvement, years	Disease duration, months	Clinical features[a]	Arterial lesions	Number of TCZ	Previous therapy	Concurrent treatment	Duration of follow-up, months	Response at week 24[b]	Surgery	The outcome of arterial imaging manifestations
10	Male/55	50	354	O, P, S	Abdominal aneurysm, stenosis of LAD/LCX/RCA	6	Pred/CYC/AZA	Pred/AZA	35	CR	Abdominal artery stenting, CABG	Uptake of FDG on coronary arteries was normal on PET after CABG surgery, and SUVmax reduced on lower abdominal aorta. Blood circulation was well after stenting surgery.

[a]O: oral ulcer; G: genital ulcer; P: pathergy test; S: skin lesions; I: intestinal ulcer; A: arthritis; U: uveitis; V: venous thrombosis. [b]CR: complete response, which was defined as the disappearance of clinical and paraclinical parameters at any time, as previously described, as well as the achievement of a CS dosage of <10 mg/day at 6 months after TCZ treatment; PR: partial response, which was defined as the improvement of clinical and paraclinical parameters as well as a reduction in the initial CS dosage of >50% at 6 months after TCZ treatment; R: relapse: was defined as newly detected appearance of organ damage or recurrence of the onset experience as well as the extreme elevation of inflammatory indicators, which required an increase in CS dosage. TCZ: tocilizumab; Pred: prednisone; TAC: tacrolimus; CA: celiac axis; SMA: superior mesenteric artery; RenA: renal artery; SCA: subclavian artery; AA: ascending aorta; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; CCA: common carotid artery; CABG: coronary artery bypass grafting; AAA: abdominal aortic aneurysm; CTA: computed tomography angiography; FDG: fluorodeoxyglucose; SUV: standard uptake value.

(40.0%) had used at least two ISs before TCZ initiation (Table 1).

All patients had painful oral ulcers, eight (80.0%) had simultaneous cutaneous lesions, four (40.0%) had genital ulcers, and one (10.0%) had concomitant symptomatic gastrointestinal ulcers. One patient had a history of uveitis, and two patients had a previous history of arthritis. No one had neurological complications. All observed vascular abnormalities included arterial aneurysm ($n = 7$), arterial stenosis ($n = 3$), and deep venous thrombosis of the lower limbs ($n = 2$). Two patients had cardiac involvement (aortic valve lesion).

At the baseline, nine patients (90.0%) were under prednisone treatment [54.5 (20.6)] mg/d. The mean number of oral ulcers, BSAS score, and BDCAF score were 3.2 (1.0), 37.4 (12.5), and 4.1 (1.1), respectively.

Efficacy of TCZ

Table 2 summarizes the patient outcomes. After 24 weeks of TCZ administration, five patients (50.0%) achieved a complete response, while four (40.0%) achieved a partial response regarding arterial lesion improvement. Radiologic improvement of arterial stenosis and aneurysms were observed in one (10.0%) and two (20.0%) patients, respectively. Five patients (50.0%) underwent successful surgical intervention, and no apparent thromboses were observed during the 24-month follow-up. Only one patient (10.0%) relapsed, exhibiting abdominal aortic aneurysm enlargement. A substantial decrease in the number of oral ulcers was observed ($P = 0.004$). On completion of the follow-up, none of the eight patients with cutaneous lesions exhibited residual impairment ($P = 0.008$). A considerable reduction in disease activity and patient-reported ratings accompanied the clinical improvement of BS-related mucocutaneous symptoms.

Clinical improvement resulted in the total withdrawal of steroids in one patient and a considerable reduction in CS dosage in the remaining eight patients. The average daily prednisone equivalent dosage decreased from 54.5 (27.2) mg/d at the baseline, to 8.3 (8.0) mg/d at week 24 ($P = 0.001$). Inflammatory markers also improved. ESR and CRP values decreased from 39.5 (29.9) mm/hand 33.0 (18.0) mg/l to 4.1 (3.2) mm/h ($P = 0.004$) and 2.8 (3.5) mg/l ($P = 0.001$), respectively. The BSAS score decreased from 37.4 (12.5) at the baseline to 10.8 (7.4) at week 24 ($P = 0.005$), whereas the BDCAF score plummeted from 4.1 (1.1) to 0.9 (0.7) ($P = 0.008$) (Fig. 1).

Side effects

In general, treatment was well tolerated, without any serious AEs. Only mild respiratory tract infections were recorded in one patient, with no trace of tuberculosis or fungal infections throughout the entire observation period.

A longer follow-up period, varying from 36 to 72 weeks, exhibited no further AEs in patients who remained on TCZ. Abdominal aneurysm reoccurred in

TABLE 2 Results at 24 weeks after tocilizumab therapy

Characteristics	Baseline	Week 24	*P* value
Steroid daily dose, *mg*	54.5 (27.2)	8.3 (8.0)	0.001
ESR, *mm/h*	39.5 (29.9)	4.1 (3.2)	0.004
CRP, *mg/L*	33.0 (18.0)	2.8 (3.5)	0.001
BSAS	37.4 (12.5)	10.8 (7.4)	0.005
BDCAF	4.1 (1.1)	0.9 (0.7)	<0.001
Patients with cutaneous disease, *n* (%)	8 (80.0)	0 (0)	0.008

BSAS: Behcet's syndrome activity score; BDCAF: Behcet's disease current activity form score.

one patient, and no probable drug-related test abnormalities were observed in any of the enrolled individuals.

Discussion

Arterial and cardiac lesions are observed in ∼10% and 5% of BS patients, respectively, thus presenting a clinical challenge [14, 15]. According to the 2018 EULAR Guidelines for the management of BS, there are no controlled data to guide treatment selection for major vascular impairment in BS [16]. Even when patients are administered sufficient immunosuppressive medicines, the prognosis remains dismal. After a median follow-up of 2 years, the complete remission rate in a cohort study of 101 BS patients with arterial lesions treated with CYC and AZA was only 38.6% [14]. TCZ has demonstrated efficacy in the treatment of large-vessel vasculitis, including Takayasu arteritis and GCA [17–22]. We conducted a prospective study in which we collected 24-week TCZ effectiveness and safety data from a group of BS patients with arterial lesions refractory to conventional treatment.

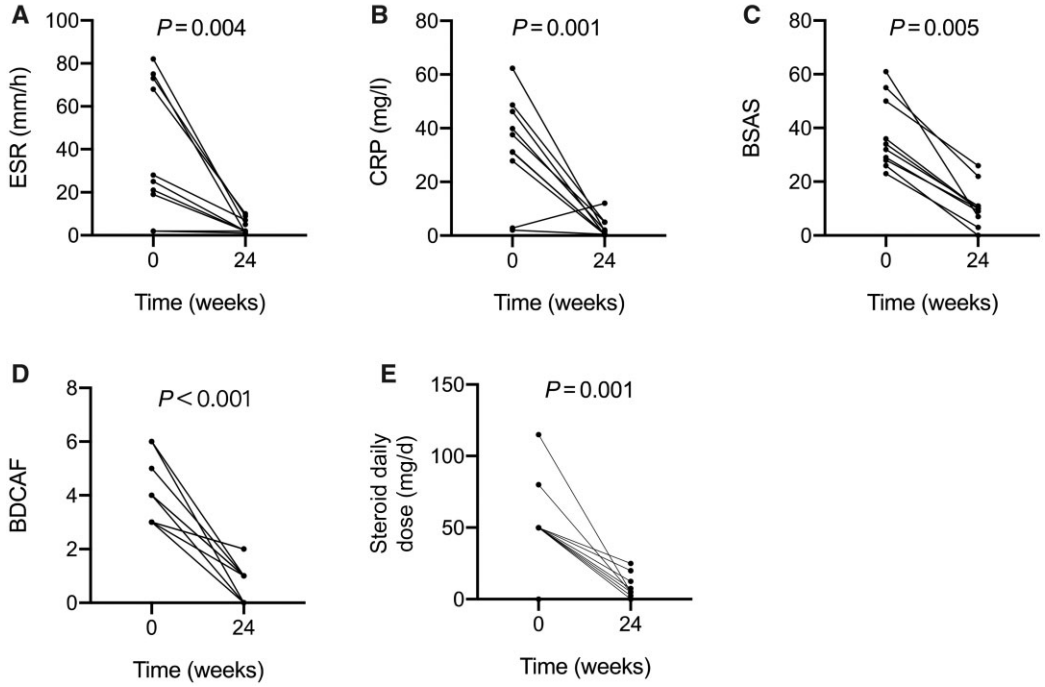
When combined with TGF-β, IL-6 has a wide range of biological effects, including inducing Th17-cell development from naïve CD4-positive T cells. Conversely, IL-6 inhibits TGF-β–induced Treg differentiation. The breakdown in balance between Th17 and Treg caused by IL-6 may be responsible for the disruption of immunological tolerance. Th17 cells release IL-17, IL-6 and TNF-α, which stimulate the entire inflammatory cascade, resulting in the development of inflammatory autoimmune diseases [23–25]. IL-6 also promotes Th22-cell differentiation and IL-22 production, which may be associated with organ involvement and BS severity [5].

Increased IL-6 concentrations have been detected in a variety of active BS patients, and have been correlated with disease activity [26]. The mechanisms by which TCZ improves clinical outcomes in BS patients who have vascular lesions are unknown. Conversely, IL-6 blockage may decrease autoantibody synthesis or rectify the Th17 imbalance [27]. TCZ is a humanized mAb that targets the soluble and membrane-bound IL-6 receptor and has been authorized for efficacy in a variety of BS complications, including ocular-, neuro-, and vasculo-BS [10]. Accordingly, Ding *et al.* demonstrated a 50% complete response in six patients with vasculo-BS unresponsive to conventional immunosuppressant therapy [28].

Despite the fact that major arterial lesions are an adverse prognostic factor for BS, anti-IL-6–based therapy was shown to be successful in 90% of (9/10) cases (partial or complete response) in our study, thus indicating that TCZ may be a potential treatment for BS-related arterial lesions when regular therapies fail. Further, our study demonstrated a significant steroid-sparing effect, with drugs being discontinued in 20% of patients, and tapered by >60% in 90% of individuals. The reduction of glucocorticoids has also been achieved with TNF antagonists in patients with uveitis associated with BS refractory to conventional immunosuppressive drugs (also along with clinical improvement) [29]. Patients in our study did not receive anti-TNF agents before TCZ for the following reasons: in patients 1 and 4, their poor cardiac function restricted the use of anti-TNF agents, as New York Heart Association class III is considered a contraindication to their use [30, 31] (TCZ had a decreased risk of major adverse cardiovascular events compared with anti-TNF agents [32]); patients 2, 5, 8 and 10 had an urgent need for surgery because their inflammation indicators had to be controlled to normal levels as soon as possible. The earlier ROSE study on treatment of RA showed that, TCZ decreased the level of CRP from (20 mg/l to 2 mg/l within 7 days [33]. In patients 3, 6, 7 and 9, the mycobacterium tuberculosis complex test (T-SPOT) result was positive, indicating a higher risk of tuberculosis infection with the use of anti-TNF agents [34]. Therefore, TCZ was a better choice for these patients. TCZ is generally a well-tolerated therapy; the main AEs associated with TCZ reported in the literature include infections, infusion-related reactions, serum lipid abnormalities, elevated transaminase levels, neutropenia, thrombocytopenia, and gastrointestinal perforation [35]. Blood counts and liver function must be monitored on a regular basis due to these risks; however, none of these AEs were observed in our study.

Interestingly, we noticed a substantial decrease in the number of oral ulcers ($P = 0.004$) observed during TCZ therapy, which is inconsistent with previous studies. Still, it is difficult to draw the conclusion that the oral ulcers were treated by the TCZ, due to the combination of other immunosuppressants; the mucocutaneous lesions had already improved after using conventional drugs, and TCZ did not aggravate them. The surgical procedures were performed as follows: the inflammatory indicators were controlled at the normal level; the diameter of the aneurysm was >5 cm; no organ failure, such as heart failure, occurred; and the patient suffered pain caused by the enlarged aneurysm, or it grew too rapidly. To some extent, the patient's improvement may have been related to the operation; however, the use of TCZ allowed for interventions to be implemented as soon as possible. Additionally, the patient's condition was controlled and stable after the operation while using TCZ. For example, patient 2 exhibited a decreased inflammatory index, with an ESR reduction from 75 mm/h to 1 mm/h, and CRP

Fig. 1 Changes in ESR, CRP, BSAS, BDCAF and steroid daily dose from baseline to 24-week follow-up



BSAS: Behcet's syndrome activity score; BDCAF: Behcet's disease current activity form score.

reduction from 46 mg/l to 0.2 mg/l; similarly, patients 5 and 8 demonstrated a decrease in the volume of the coronary aneurysm before surgery.

It is known that BS usually abates with age. In patient 3, we considered that the aortic aneurysm had occurred due to BS, since he exhibited no risk factors for atherosclerosis—such as a history of smoking or early family history of coronary heart disease—and his low-density lipoprotein level was normal. In patient 4, coronary stenosis may have been related to atherosclerosis to some extent, as he had a history of smoking and hypertension. Still, we believe the presence of vasculitis to be an important pathogenic factor, since stenosis had reoccurred after coronary stent implantation using regular secondary preventive drugs, such as antiplatelets, beta-blockers, and lipid-lowering drugs. Additionally, the CT angiography images showed irregular aortic wall morphology, penetrating ulcers, and many small ulcers scattered in the aorta, indicating vasculitis.

Our study has certain limitations. Owing to the rarity of arterial involvement in BS, the cohort size was relatively small. Conventional treatments received before TCZ initiation, despite their stable doses, might have been heterogeneous, and the lack of a placebo arm due to the real-world setting might have led to bias. Nevertheless, our study, which was based on daily practice, emphasizes the positive effect and therapeutic safety of TCZ in refractory BS patients with major artery involvement, thus serving as a potential launching pad for larger multicentre studies. Further prospective controlled clinical trials are warranted to confirm the effectiveness and safety of TCZ.

Conclusion

Our findings suggest that TCZ treatment is safe and effective, and has a beneficial outcome in BS patients with refractory arterial lesions, as well as a favourable steroid- and immunosuppressant-sparing effect. TCZ is thus a potential treatment option for BS patients with refractory arterial impairment.

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Data availability statement

Data are available upon reasonable request from the corresponding author.

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