Tocilizumab in the treatment of severe and refractory parenchymal neuro-Behçet's syndrome: case series and literature review

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Abstract

Objectives: This study aimed to investigate the efficacy and safety of tocilizumab (TCZ) in severe and refractory parenchymal neuro-Behçet's syndrome (p-NBS).

Methods: We retrospectively analyzed five patients with p-NBS treated with TCZ in our center between 2013 and 2020, and six cases from literature research with the index terms "neuro-Behçet's syndrome" and "tocilizumab" on PubMed NCBI.

Results: A total of 11 patients with p-NBS were enrolled (5 males, 6 females), with a mean age of 34.5 ± 8.0 years at the onset. All the patients had parenchymal neurological lesions, six patients (54.5%) suffered from multiple lesions, and nine patients (81.8%) were disabled. Before TCZ administration, all the patients had failed conventional therapy, eight patients (72.7%) received two or more immunosuppressants, and five patients showed insufficient response or intolerance to other biologics. TCZ was administrated at 8 mg/kg every 4 weeks, with background glucocorticoids (GCs) and immunosuppressants. After a median follow-up of 13 (interquartile range, 3.5–23.5) months, all the patients achieved both clinical and radiological improvements, and the Behçet's Disease Current Activity Form score improved significantly (3 *versus* 0, median, $p = 0.004$), the Rankin score also decreased (4 *versus* 2, median, $p = 0.005$). Levels of interleukin-6 in the cerebrospinal fluid decreased significantly in five patients (533.4 ± 389.7 pg/ml *versus* 34.5 ± 27.1 pg/ml, $p = 0.048$), after a median of two (interquartile range, 1–4) times of TCZ infusions. Furthermore, the GC dosage (*per os*) reduced from 69.2 ± 16.9 mg/d to 16.4 ± 16.2 mg/d ($p = 0.000$), and immunosuppressants were tapered in number and dosage in seven (63.6%) and four (36.3%) patients, respectively. No serious adverse events or deaths were observed during follow-up.

Conclusions: TCZ is well tolerated and effective in severe and refractory p-NBS, with a favorable GC- and immunosuppressant-sparing effect. Cerebrospinal fluid interleukin-6 might be used to monitor the effects of TCZ in p-NBS.

Keywords: Behçet's syndrome, neurological involvement, tocilizumab

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Introduction

Behçet's syndrome (BS) is a multifactorial polygenic autoinflammatory disorder characterized by multi-organ involvement, presenting different phenotypic clusters.[1] Neurological involvement, so-called neuro-Behçet's syndrome (NBS), is one of its life-threatening manifestations with high mortality and severe disability.[2,3] The frequency of NBS among patients with BS is approximately 9% (ranging 3–30%).[4] Generally, there are two categories of NBS: parenchymal (p-NBS) and nonparenchymal involvement.[5–8] The former involves meningoencephalitis, which can cause significant neurological consequences from cognitive changes to paralysis, with brain stem involvement as the most characteristic feature;

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the latter refers to the vascular phenotype, involving intracranial arteries and venous sinuses. Glucocorticoids (GCs) and immunosuppressants remain to be the cornerstones for NBS management. The international consensus recommendations of p-NBS[7] suggested that tumor necrosis factor (TNF)-α inhibitors could be alternatives as second-line therapies when conventional therapy is ineffective or intolerable. In addition, the 2018 European League Against Rheumatism guidelines recommend that TNF-α inhibitors be considered first-line therapy in severe and (or) refractory p-NBS.[9] However, issues including inadequate response, loss of the initial efficacy over time, intolerance, and relative contraindications limited the use of TNF-α inhibitors, which necessitated seeking alternative therapies to treat severe or refractory p-NBS. Although growing evidence supported the advantage of interleukin (IL)-6 receptor antagonist tocilizumab (TCZ) in treating refractory BS,[10,11] only case studies reported the treatment of TCZ in NBS. In this study, we aimed to elucidate the efficacy and safety of TCZ in p-NBS.

Methods

Patients

We retrospectively analyzed the clinical data of refractory patients with NBS treated with TCZ in our center from January 2013 to January 2020. All the patients fulfilled the International Criteria for BD (ICBD).[12] The diagnosis of neurological involvement was made by two rheumatologists and two neurologists, based on neurological symptoms, physical examination, cerebrospinal fluid (CSF) analysis, and neuroradiological examinations, adhering to the classification criteria of the 2014 International Consensus on NBS[7] and were categorized as p-NBS. Clinical data including demographics, clinical features, laboratory tests, imaging, treatment, and outcome measures were retrospectively collected. We also searched and summarized the papers with the index terms "neuro-Behçet's syndrome" and "tocilizumab" on PubMed NCBI.[13–16]

The clinical response and safety of TCZ treatment were evaluated. Complete response (CR) was defined by the disappearance of all neurological symptoms and by the improvement of radiological abnormalities related to NBS 6 months after TCZ treatment. Partial remission (PR) was defined by the improvement of neurological symptoms and of radiological abnormalities 6 months after TCZ treatment or by a decrease of >50% of the GC dose as compared with baseline. Other patients were considered nonresponders.[17] We chose the modified Rankin score to assess the disability status of patients with NBS. Severe NBS was defined as Rankin score ⩾3.[18] The BS disease activity was assessed according to the BD Current Activity Form (BDCAF) 2006 (http://www.behcet.ws/pdf/BehcetsDiseaseActivityForm.pdf).

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital. All participants signed written informed consent.

Statistical analysis

Statistical analysis was performed with SPSS version 21.0 (IBM Inc., Armonk, USA). Categorical variables were presented with counts and proportions. Data with Gaussian distribution were described as mean ± SD and non-Gaussian distributed data were described as median and range. The continuous variables were analyzed by the paired sample *t*-test. Non-Gaussian distributed data and Ranked ordinal data were analyzed by the Wilcoxon signed-rank test, and the correlation was performed with Spearman's rank correlation test. A value of $p < 0.05$ was considered significant.

Result

Epidemiology

A total of 11 patients with p-NBS were enrolled (5 patients from our center and 6 patients from the literature), including 6 males and 5 females. The mean age of onset of BS and NBS was 24.8 ± 8.4 and 34.5 ± 8.0 years, respectively.

BS manifestations

In these patients, oral ulceration was presented in all, followed by skin lesions (8 of 11, 72.7%) (including pseudo folliculitis, nodular erythema or positive pathergy test), genital ulcers (7 of 11, 63.6%), uveitis (3 of 11, 27.3%), arthritis (2 of 11, 18.2%) and vascular involvement (2 of 11, 18.2%), presented as deep vein thrombosis.

Neurological features

Clinical features. All the patients showed parenchymal lesions, which involved the hemisphere (7

of 11, 63.6%), brainstem (5 of 11, 45.5%), spinal cord (5 of 11, 45.5%) and cerebellum (1 of 11, 9.1%). Six cases (54.5%) suffered from multiple lesions. One patient was complicated with peripheral neuropathy.

The most common clinical symptoms were headache (72.7%), followed by disturbance of urine (54.5%, including urinary incontinence in four cases, urinary retention in two cases), fevers, visual loss and numbness of extremities (36.4% each), dysarthria (27.3%), epilepsy (18.2%), psychological and behavioral change, irritating cough, conscious disturbance and cognitive dysfunction (9.1% each). Nine patients (81.8%) became disabled due to muscle weakness or dyskinesia (Table1). The median Rankin score was 4.

Neurological imaging. All patients received neurological magnetic resonance imaging (MRI) examination and showed parenchymal lesions, which were hyperintense on T2-weighted images in seven patients (details of MRI lacked in the other four cases). Of all the lesions, the brainstem was involved in 5 patients (5 of 11, 45.5%), followed by the thalamus and the basal ganglia (3 of 11, 27.3% each), the periventricular, the semi-oval center and the internal capsule (2 of 11, 18.2% each), and the cerebellum, the temporal lobe and the parietal lobe (1 of 11, 9.1% each). Five patients showed abnormal signals in the spinal cord (including cervical cord involvement in two and thoracic cord involvement in three), one of them demonstrated concurrent post-contrast enhancement and atrophic change of the thoracic cord.

CSF analysis. The CSF tests were abnormal in all but one patient among the nine patients tested. The CSF pressure was increased in three patients, ranging from 230 to 330 mmH_2O. CSF protein was mildly elevated in seven cases (77.8%), with a median level of 0.64 (0.61–1.22) g/L. Five cases (55.6%) showed pleocytosis, with lymphocyte predominance in two cases, polynuclear predominance in one case, details of the rest two cases are lacking. The CSF IL-6 levels were elevated in six patients (mean concentration 533.4 ± 389.7 pg/ml), including all five patients from our center (cases 1–5), whereas the serum IL-6 was within the normal range (mean concentration 6.2 ± 5.6 pg/ml). Of the five patients with CSF IL-6 level tested sequentially, it correlated with BDCAF 2006 score ($r = 0.698$, $p = 0.017$).

Previous treatment

Before TCZ, all patients had received GCs and immunosuppressants. Seven patients (63.6%) received methylprednisolone pulse therapy. In terms of immunosuppressants, they were cyclophosphamide (CTX) in eight cases, azathioprine (AZA) in six cases, methotrexate (MTX) in five cases, cyclosporine A (CsA) in two cases, tacrolimus and mycophenolate mofetil in one each. Eight patients (72.7%) received more than one immunosuppressant. Intrathecal injection of dexamethasone 10 mg and MTX 10 mg were administrated in five patients. All patients had a poor clinical response to conventional treatment.

In combination with conventional GCs and immunosuppressants, five patients received biological agents, including infliximab (IFX) ($n = 5$), interferon (IFN)-α2a ($n = 3$) and daclizumab ($n = 1$). One patient showed no response to daclizumab or IFN-α2a, though IFX effectively induced clinical improvements, it was discontinued due to immunoglobulin (Ig)A nephropathy. The other four patients received IFX, among whom two had poor responses and another two relapsed during GC tapering. IFN-α2a was ineffective in two patients who did not respond well to IFX.

All patients responded inadequately despite the above intensive therapy. Besides, one patient suffered hepatic dysfunction after CTX therapy (case 2), two patients were complicated with latent tuberculosis (cases 1 and 2).

Treatment and outcome of TCZ

The dosage of TCZ infusions was 8 mg/kg every 4 weeks. After a mean follow-up of 13.1 ± 10.2 months, all patients improved both clinically and radiologically. Two patients achieved CR and the other nine achieved PR. The lesions disappeared in four patients and attenuated considerably in three on follow-up MRI [Figure 1 (a,b)]. The BDCAF score decreased significantly (3 *versus* 0, median, $p = 0.004$), [Figure 1(c)]. The Rankin score also decreased from a median of 4 at the initiation of TCZ to 2 at the last visit ($p = 0.005$) [Figure 1(d)], five patients with disabilities recovered partially and could stroll for a few meters. Follow-up CSF IL-6 analysis was performed in five patients, which decreased significantly after a median of 2 (1–4) times of TCZ infusions (533.4 ± 389.7 pg/ml *versus* 34.5 ± 27.1 pg/ml, $p = 0.048$) [Figure 1(e)]. The GC dosage (of prednisone or equivalent) reduced significantly from 69.2 ± 16.9 mg/day at

Table1. Tocilizumab therapy in the eleven cases of severe and refractory NBS.

			Clinical manifestations of NBS			Previous treatment			Treatment of TCZ			
Case	**Sex/ age**	**Clinical features**	**Symptoms**	**Lesions sites**	**CSF tests**	**Conventional therapy**	**Biological agents**	**Drug combination**	**Follow-up (months)**	**Outcome**	**Radiological change**	**Side effect**
1	M/38	O, G	fever, headache, visual loss, urinary incontinence, muscle weakness, numbness	Spinal cord (cervical cord and thoracic cord)	ICP 230 mmH_2O, Pro0.64 g/L, IL-6 187 pg/ml	GC CTX MTX	None	GC CTX MTX	13	PR	Improvement	None
2	M/27	O, G, S, U	fever, dysarthria, irritating cough, muscle weakness, numbness	Brainstem, Hemicerebrum	ICP 330 mmH_2O, WBC 192 × 10^6/L, Pro1.22 g/L, IL-6 1000 pg/ml	GC CTX MTX	None	GC MTX	2	PR	/	None
3	M/28	O, G, U	headache, urinary incontinence, muscle weakness	Thoracic cord Peripheral neuropathy	ICP 140 mmH_2O, WBC 8 × 10^6/L, Pro0.69 g/L, IL-6 238 pg/ml	GC CTX MTX	None	GC CTX MTX	3	PR	/	None
4	M/38	O, G, S, A	conscious disturbance, psychological and behavioral change, muscle weakness	Brainstem Hemicerebrum Cervical cord	ICP 110 mmH_2O, WBC 70 × 10^6/L, Pro0.61 g/L, IL-6 332 pg/ml	GC CTX AZA	None	GC AZA	14	PR	Clear regression	None
5	F/42	O, G	headache, dysarthria, epilepsy, cognitive dysfunction, muscle weakness, urinary incontinence	Hemicerebrum	ICP 240 mmH_2O, WBC 6 × 10^6/L, Pro0.81 g/L, IL-6 219 pg/ml	GC MTX CTX	None	GC MTX CTX	2	PR	stable	None
6[13]	M/30	O, S, U	fever, headache	Brainstem Hemicerebrum	pleocytosis	GC CTX MMF CsA AZA MTX	daclizumab IFN-α2a IFX	GC	7	CR	Clear regression	None
7[14]	F/26	O, S	fever, headache, epilepsy	Brainstem Hemicerebrum Cerebellum	Normal	GC AZA	None	GC	21	CR	Clear regression	None
8[15]	F/24	O, G, S, A	visual loss, muscle weakness, dyskinesia, numbness, uroschesis	Hemicerebrum	N/A	GC CTX FK-506 AZA	IFN-α2a IFX	GC	26	PR	/	None
9[15]	F/48	O, S, V	headache, visual loss, muscle weakness, urinary incontinence	Hemicerebrum	N/A	GC CTX AZA	IFN-α2a IFX	GC	26	PR	Stable	None
10[15]	F/36	O, S	headache, visual loss, dysarthria, muscle weakness	Brainstem Spinal cord	pleocytosis, Pro0.62 g/L	GC CsA	IFX	GC	26	PR	Stable	None
11[16]	M/43	O, G, S, V	dyskinesia, numbness, uroschesis	Thoracic cord	pleocytosis, Pro0.62 g/L	GC AZA	IFX	GC AZA	4	PR	Clear regression	None

Normal values of CSF lab tests: CSF IL-6 < 5.9 pg/ml; WBC 0–8 × 10^6/l; Pro 0.15–0.45 g/l.
A, arthritis; AZA, azathioprine; CR, complete response; CsA, cyclosporine A; CSF, cerebrospinal fluid; CTX, cyclophosphamide; F, female; FK-506, tacrolimus; G, genital ulcer; GC, glucocorticoid; ICP, intracranial pressure; IFN, interferon; IFX, infliximab; M, male; MMF, mycophenolate mofetil; MTX, methotrexate; N/A, unavailable; NBS, neuro-Behçet's syndrome ; O, oral ulcer; PR, partial remission; Pro, protein; S, skin lesions; TCZ, tocilizumab; U, uveitis; V, vascular involvement; WBC, white blood cell.

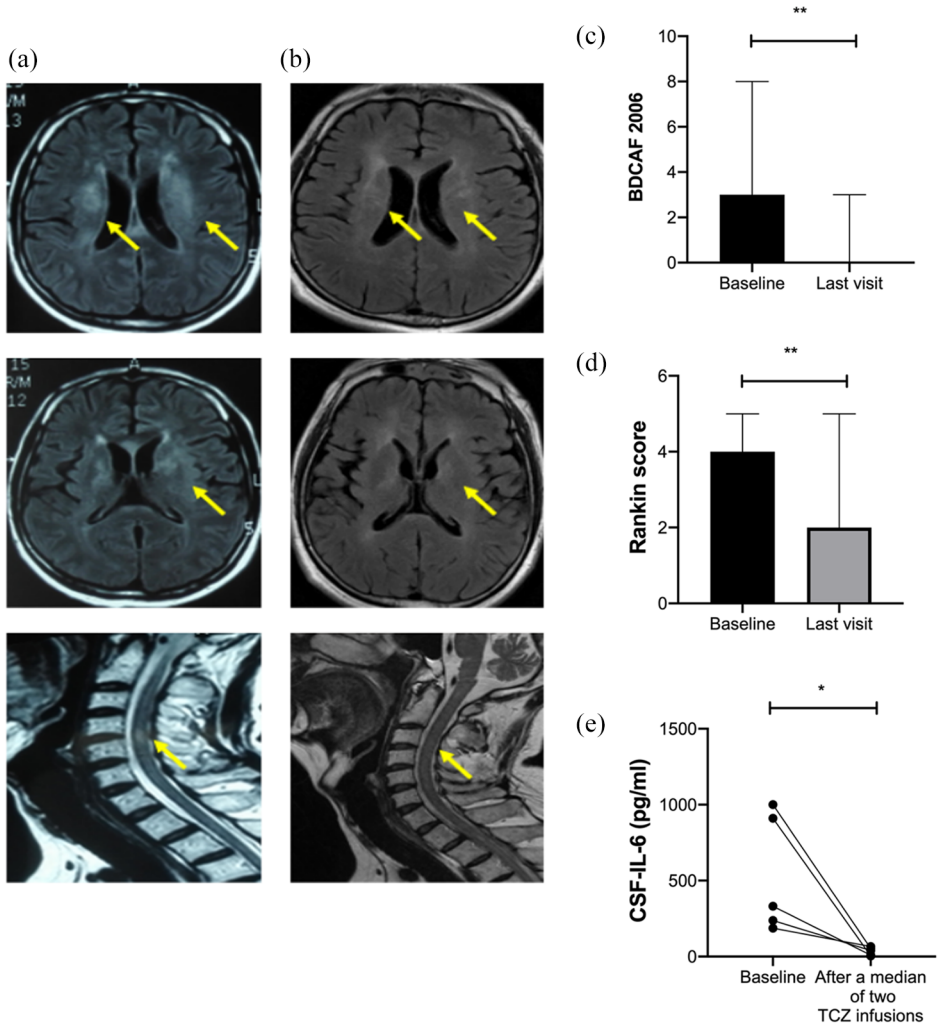

Figure 1. The outcome of patients with severe and refractory NBS treated with TCZ. (a) High-intensity lesions in the bilateral corona radiata, lateral ventricle, and cervical spinal cord C4-5 on T2 Flair images at baseline. (b) The lesions were significantly attenuated after two TCZ infusions. (c) The BDCAF score at baseline and at the last visit. (d) The Rankin score at baseline and at the last visit. (e) CSF IL-6 concentration at baseline and after a median of 2 (1–4) times of TCZ infusions.
BDCAF, Behçet's Disease Current Activity Form; CSF, cerebrospinal fluid; IL, interleukin; NBS, neuro-Behçet's syndrome; TCZ, tocilizumab.

the initial state to 16.4 ± 16.2 mg/day at last visit ($p = 0.000$). Three patients withdrew GCs during follow-up with no relapses. Besides, the concomitant immunosuppressants were MTX ($n = 3$), CTX ($n = 3$), AZA ($n = 2$), and three patients received two concurrent immunosuppressants. They were tapered in number and dosage in seven (63.6%) and four patients (36.3%), respectively.

During the follow-up period, one patient relapsed after the eighth TCZ infusion and regained improvement after oral MTX at 10 mg per week was added. One patient relapsed after 18 months of TCZ infusion and was adjusted to TCZ 8 mg/kg every other week. The symptoms improved after three infusions and remained stable at the last visit. In terms of side effects, we have not detected any serious infection or allergic reaction. With tuberculosis (TB) prophylaxis in patients with latent infection, no active TB was observed.

Discussion

The various phenotypic clusters of BS suggest that different pathogenetic mechanisms operate in the disease, thus "BS" is a more proper annotation than "Behçet's disease".[9,19,20] Among the different phenotypes, p-NBS is one of the leading

causes of morbidity and mortality in BS. Our previous study showed that the mortality of p-NBS was 11.1%.[21] So far, there are no randomized controlled trials regarding NBS therapy. In this article, we described 11 patients with refractory p-NBS who had an inadequate response to conventional therapies and/or biological agents. Our data showed that TCZ could improve the clinical symptoms in patients with severe and refractory p-NBS with a favorable steroid- and immunosuppressant-sparing effect. Five patients had a rapid CSF IL-6 decrease after a median of two TCZ infusions, indicating a rapid effect of TCZ.

The pathogenesis of NBS remains unknown. In contrast to the large-vascular form that presents with cerebral venous sinus thrombosis, p-NBS is considered a small vascular disease mostly affecting the postcapillary venules. A recent study demonstrated the role of type 17 helper T cells, IL-6, and TNF-α in the pathogenesis of BS.[22] The histopathology of NBS[23] suggested that pro-inflammatory cytokines produced by infiltrating T lymphocytes and monocytes, such as IL-6, might result in neuronal apoptosis. These indicate that specific cytokines might be potential targets for the treatment of NBS.

IL-6 is a multifunctional cytokine involved in immune regulation, hematopoiesis, inflammation, and neural development, and it has a major role in the brain's response to injury. Neurons, astrocytes, microglia, and endothelial cells are the essential sources of IL-6 in the central nervous system. CSF concentrations of IL-6 are elevated in many autoimmune diseases, including neuropsychiatric systemic lupus erythematosus,[24] neuromyelitis optica, and multiple sclerosis. TCZ, an anti-IL-6R monoclonal antibody, was proved a promising therapeutic option for the latter two.[25]

IL-6 plays an essential role in BS. Several studies have demonstrated that IL-6 level was elevated in various phenotypes of active BS, and its serum and vitreous fluid levels correlated with disease activity in acute ocular-BS.[26] Consistent with previous studies, the CSF IL-6 level elevated markedly in patients with active p-NBS, who were more likely to have increased CSF cell counts and protein levels,[7,27–29] so we tested CSF IL-6 sequentially while performing intrathecal therapy. As expected, our data demonstrated that elevated CSF IL-6 level was correlated with BDCAF 2006 score, the BS disease activity index. Thus, the CSF IL-6 level might be a potential intervention target for p-NBS. TCZ has been used in BS successfully and widely, such as in ocular-BS[30] and vasculo-BS.[11] However, it is ineffective in treating BS cases with arthritis or gastrointestinal involvement.[31] The discrepancy may be related to the differently activated inflammatory signaling pathways in various phenotypes of the disease.

Herein, we showed 11 patients with p-NBS with a high Rankin score at baseline. More than half of them had multiple neurological lesions, and the severe disability rate was 81.8%. All of them had an inadequate response to conventional therapies, some had received biologics but stopped due to inefficacy or intolerance. Our study demonstrated that TCZ could improve clinical symptoms and decrease CSF IL-6 levels in patients with p-NBS rapidly and efficiently, suggesting that CSF IL-6 could be used to monitor the effects of TCZ in p-NBS.

The most common adverse effect of TCZ is an infection, such as gastroenteritis and pneumonia.[32] Considering the potential risk of TB reactivation of IFX,[33] two patients with latent TB were treated with TCZ. None of the common adverse effects or reactivation of TB was observed in our patients. In general, TCZ is safe in long-term treatment. Moreover, our study showed TCZ has a favorable steroid- and immunosuppressant-sparing effect, which was especially beneficial for patients with refractory BS at risk of side effects with a high cumulative dose of corticosteroids and multiple immunosuppressants.

Our study's limitations lie in its retrospective design following a small number of cases and the limited data from the literature. We could not analyze the dynamic change of serum inflammatory markers after TCZ treatment. Besides, our study revealed the potential of the GC- and immunosuppressant-sparing effect of TCZ. However, the assessment's effectiveness was insufficient due to the short-term follow-up and the moderate GC doses in some individuals. Further long-term studies are warranted to confirm the therapeutic potential of TCZ in NBS.

In conclusion, in combination with GCs and immunosuppressants, TCZ is a promising choice for severe and refractory p-NBS. CSF IL-6 might be used to monitor the effects of TCZ in p-NBS.

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Author contributions

All authors made substantial contributions to this study. Jinjing Liu, Yunjiao Yang, Shangzhu Zhang, Di Wu, Lingyi Peng acquired the data, Dong Yan and Jinjing Liu performed the data analysis and drafted the manuscript. Wenjie Zheng provided critical revisions to the manuscript. Zhimian Wang, Zhichun Liu also reviewed the manuscript and provided valuable feedback. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics approval

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (approval number: S-443). All the patients from our center provided written informed consent in accordance with the Declaration of Helsinki.

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References

1. Krainer J, Siebenhandl S and Weinhäusel A. Systemic autoinflammatory diseases. *J Autoimmun* 2020; 109: 102421.
2. Hirohata S, Kikuchi H, Sawada T, *et al.* Retrospective analysis of long-term outcome of chronic progressive neurological manifestations in Behçet's disease. *J Neurol Sci* 2015; 349: 143–148.
3. Kural-Seyahi E, Fresko I, Seyahi N, *et al.* The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine (Baltimore)* 2003; 82: 60–76.
4. Borhani-Haghighi A, Kardeh B, Banerjee S, *et al.* Neuro-Behçet's disease: an update on diagnosis, differential diagnoses, and treatment. *Mult Scler Relat Disord* 2019; 39: 101906.
5. Akman-Demir G, Serdaroglu P and Tasçi B. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. *Brain* 1999; 122: 2171–2182.
6. Al-Araji A and Kidd DP. Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. *Lancet Neurol* 2009; 8: 192–204.
7. Kalra S, Silman A, Akman-Demir G, *et al.* Diagnosis and management of neuro-Behçet's disease: international consensus recommendations. *J Neurol* 2014; 261: 1662–1676.
8. Uygunoğlu U and Siva A. Behçet's syndrome and nervous system involvement. *Curr Neurol Neurosci Rep* 2018; 18: 35.
9. Hatemi G, Christensen R, Bang D, *et al.* 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; 77: 808–818.
10. Muselier A, Bielefeld P, Bidot S, *et al.* Efficacy of tocilizumab in two patients with anti-TNF-alpha refractory uveitis. *Ocul Immunol Inflamm* 2011; 19: 382–383.
11. Ding Y, Li C, Liu J, *et al.* Tocilizumab in the treatment of severe and/or refractory vasculo-Behçet's disease: a single-centre experience in China. *Rheumatology (Oxford)* 2018; 57: 2057–2059.
12. (ITR-ICBD) International Team for the Revision of the International Criteria for Behçet's Disease, Davatchi F, AssaadKhalil S, *et al.* The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014; 28: 338–347.
13. Shapiro LS, Farrell J and Borhani-Haghighi A. Tocilizumab treatment for neuro-Behçet's disease, the first report. *Clin Neurol Neurosurg* 2012; 114: 297–298.
14. Essaadouni L and Ha-ou-nou FZ. Efficacy and safety of tocilizumab in neuro-Behçet's disease: a case report. *Rev Neurol (Paris)* 2017; 173: 171–172.

15. Addimanda O, Pipitone N, Pazzola G, *et al*. Tocilizumab for severe refractory neuro-Behçet: three cases IL-6 blockade in neuro-Behçet. *Semin Arthritis Rheum* 2015; 44: 472–475.

16. Urbaniak P, Hasler P and Kretzschmar S. Refractory neuro-Behçet treated by tocilizumab: a case report. *Clin Exp Rheumatol* 2012; 30: S73–S75.

17. Desbois AC, Addimanda O, Bertrand A, *et al*. Efficacy of anti-TNFa in severe and refractory neuro-behçet disease: an observational study. *Med (United States)* 2016; 95: e3550.

18. Noel N, Bernard R, Wechsler B, *et al*. Long-term outcome of neuro-behçet's disease. *Arthritis Rheumatol* 2014; 66: 1306–1314.

19. Sota J, Rigante D, Emmi G, *et al*. Behçet's syndrome in Italy: a detailed retrospective analysis of 396 cases seen in 3 tertiary referral clinics. *Intern Emerg Med*. Epub ahead of print 1 February 2020. DOI: 10.1007/s11739-019-02248-4

20. Yazici H, Seyahi E, Hatemi G, *et al*. Behçet syndrome: a contemporary view. *Nat Rev Rheumatol* 2018; 14: 107–119.

21. Yan D, Liu JJ, Zhang Y, *et al*. The clinical features and risk factors of parenchymal neuro-behçet's disease. *J Immunol Res* 2019; 2019: 7371458.

22. Lopalco G, Lucherini OM, Lopalco A, *et al*. Cytokine signatures in mucocutaneous and Ocular Behçet's disease. *Front Immunol* 2017; 8: 200.

23. Hirohata S. Histopathology of central nervous system lesions in Behçet's disease. *J Neurol Sci* 2008; 267: 41–47.

24. Hirohata S and Miyamoto T. Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. *Arthritis Rheum* 1990; 33: 644–649.

25. Hofer MJ and Campbell IL. Immunoinflammatory diseases of the central nervous system - the tale of two cytokines. *Br J Pharmacol* 2016; 173: 716–728.

26. Ozdamar Y, Berker N, Bahar G, *et al*. Inflammatory mediators and posterior segment involvement in ocular Behçet disease. *Eur J Ophthalmol* 2009; 19: 998–1003.

27. Hirohata S and Kikuchi H. Changes in biomarkers focused on differences in disease course or treatment in patients with neuro-Behçet's disease. *Intern Med* 2012; 51: 3359–3365.

28. Hirohata S, Isshi K, Oguchi H, *et al*. Cerebrospinal fluid interleukin-6 in progressive neuro-Behçet's syndrome. *Clin Immunol Immunopathol* 1997; 82: 12–17.

29. Akman-Demir G, Tüzün E, Içöz S, *et al*. Interleukin-6 in neuro-Behçet's disease: association with disease subsets and long-term outcome. *Cytokine* 2008; 44: 373–376.

30. Alokaily F, Al Saati A and Jawad A. Successful treatment of Behçet's uveitis with Tocilizumab. *Saudi J Ophthalmol* 2017; 31: 42–44.

31. Deroux A, Chiquet C and Bouillet L. Tocilizumab in severe and refractory Behçet's disease: four cases and literature review. *Semin Arthritis Rheum* 2016; 45: 733–737.

32. Nakaoka Y, Isobe M, Tanaka Y, *et al*. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. *Rheumatology* 2020; 17: kez630.

33. Miller EA and Ernst JD. Anti-TNF immunotherapy and tuberculosis reactivation: another mechanism revealed. *J Clin Invest* 2009; 119: 1079–1082.