Infliximab for parenchymal neuro-Behçet's syndrome: case series and meta-analysis

X. Wang[1], Y. Liu[1], Y. Ao[1], J. Wang[2], J. Liu[1], Y. Xu[3], W. Zheng[1]

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; National Clinical Research Center for Dermatologic and Immunologic Diseases, Ministry of Science & Technology, Beijing, China;
[2]Department of Neurology, Beijing Tiantan Hospital, China National Clinical Research Center for Neurological Diseases, Capital Medical University, Beijing, China;
[3]Department of Neurology, Peking Union Medical College Hospital, Beijing, China.

Abstract

Objective

This study aims to evaluate the efficacy and safety of infliximab (IFX) in patients with parenchymal neuro-Behçet's syndrome (p-NBS).

Methods

We retrospectively analysed eleven p-NBS patients treated with IFX at our institution and combined them with studies from database searches for a meta-analysis. Pooled estimates of clinical response (complete and partial remission) and MRI improvement at months 3, 6, and 12 were calculated.

Results

One patient achieved CR and the other ten patients achieved PR at our institution. 8 studies (77 patients) were included in the meta-analysis. At 3, 6, and 12 months, 97% (95%CI 61.9–100%), 89.6% (95%CI 45.9–100%), 100% (95%CI 96.0–100%) of patients showed clinical response and 100% (95%CI 89.7–100%), 89.1% (95% CI 26.3-100%), 99.5% (95% CI 96.0–100%) of patients showed radiological improvement, respectively. Severe adverse events were observed in 7 patients.

Conclusion

IFX was effective and relatively safe for p-NBS. Patients should be re-evaluated after 3 months of IFX to determine further therapy.

Key words

neuro-Behçet's syndrome, infliximab, anti-TNF-α agents, therapeutic efficacy

*Xiaoou Wang, MD**
*Yeling Liu, MD**
*Yiyuan Ao, MD**
Jing Wang, MD
Jinjing Liu, MD
Yan Xu, MD
Wenjie Zheng, MD

**Contributed equally to this work.*

Please address correspondence to:
Wenjie Zheng
Department of Rheumatology and Clinical Immunology,
Peking Union Medical College Hospital,
Shuai Fu Yuan No.1, East District,
100730 Beijing, China.
E-mail: zhengwj@pumch.cn

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Introduction

Behçet's syndrome (BS) is a chronic, recurrent systemic vasculitis that can affect multiple systems (1). One of its most severe manifestations is neuro-Behçet's syndrome (NBS), which affects approximately 9% of BS patients (ranging from 3–30%) (2). NBS can be divided into two main categories: parenchymal NBS (p-NBS) manifestations including lesions in the brainstem, hemisphere, spinal cord, and meningoencephalitis, and non-parenchymal NBS (non-pNBS) manifestations, including cerebral vascular involvement. P-NBS (75–80% of NBS) (3) results in severe neurological consequences with a poorer prognosis, ranging from cognitive changes to paralysis, which remains a challenging clinical issue (4, 5).

Conventional treatment of p-NBS is based on glucocorticoids (GCs) and immunosuppressive agents such as azathioprine or cyclophosphamide; however, the non-response rate to conventional therapy remains high. In recent years, monoclonal anti-tumour necrosis factor-alpha (TNF-α) antibodies such as infliximab (IFX) have been reported in several studies with moderate efficacy (6-13), and were recommended as the first-line therapy for severe p-NBS or in refractory patients in the 2018 European League Against Rheumatism (EULAR) guidelines (14). Additionally, the Japanese National Research Committee claimed in 2020 that IFX is a plausible option for both acute and chronic progressive NBS patients with insufficient response to conventional therapy (15). However, these recommendations are based on small sample sizes with case series or single-arm retrospective observational studies, and the duration of efficacy evaluation is highly heterogeneous, still lacking a high level of evidence. Hamdy and Woldeamanuel (16) recently conducted a meta-analysis showing a good pooled efficacy of IFX in treating NBS. However, their study lacked a detailed time analysis for a clearer IFX effect timeline in NBS treatment and did not classify the two types of NBS (p-NBS and non-pNBS). Therefore, further research is needed to address these gaps.

In this paper, we retrospectively analysed the clinical data of eleven patients in our cohort with severe and/or refractory p-NBS treated with IFX. Besides, a single-arm meta-analysis was carried out including the results from our institution. We aimed to investigate the efficacy and safety of IFX in the whole course of p-NBS treatment at 3, 6 and 12 months, which will hopefully provide better evidence for the management of p-NBS.

Methods

Case series

A retrospective case series was conducted to analyse the effect of IFX in severe and/or refractory p-NBS in Peking Union Medical College Hospital (PUMCH) from January 2016 to April 2023. All the patients fulfilled the 2013 International Criteria for Behçet's Disease (ICBD) (17). NBS was diagnosed by two rheumatologists and two neurologists, using the 2014 International Consensus Recommendation (ICR) criteria for NBS and was classified as definite or probable NBS with parenchymal involvement (5). Clinical data were retrospectively collected, including demographics, clinical features, laboratory tests, imaging, treatment, and outcome measures.

Therapeutic efficacy was evaluated by the degree of clinical and radiological improvement. The outcomes were defined as:

i) clinical response (9, 18): a) complete remission (CR): the resolution of NBS-related symptoms; b) marked clinical improvement (partial remission, PR): an improvement in NBS-related symptoms; c) No response (NR): Patients not meeting the criteria for CR or PR.

ii) Radiological outcome (6, 11): improvement and no new-onset imaging findings compared to baseline.

Other evaluations include GCs and immunosuppressants-sparing effects; BS disease activity accessed by Behçet's Disease Current Activity Form (BDCAF) 2006 and Modified Rankin score to assess the disability status of NBS patients (Rankin score≥3 was considered severe patients). These were evaluated at 3 months, 6 months, 12 months and longer.

Therapeutic efficacy in our cohort was also assessed according to the "Hamdy and Woldeamanuel Simple Response Score, 2020" (16). The score included clinical and radiographic criteria as well as CSF analysis, resulting in a total score from 0 to 5.

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (ZS-2098). All the patients from our centre provided written informed consent in accordance with the Declaration of Helsinki.

Meta-analysis

- Search strategy

This meta-analysis followed the "Preferred Reporting Item for System Evaluation and Meta analysis" (PRISRM) guidelines. We have registered on PROSPERO with the ID of CRD42023424770. Two investigators (LYL and AYY) independently searched and screened literature and double assessed by another investigator (WXO). PubMed, Embase, Cochrane Library and Web of Science were systematically searched using the following logics: Behçet's syndrome (all synonyms) AND Infliximab (all synonyms) AND ('neuro' OR 'neurological' OR 'neurologic') (last search: 25 October 2022). The details of our search strategy were shown in Supplementary Table S1. The reference list of included articles was filtered manually to avoid missing any eligible studies.

- Study selection and data extraction

The following criteria were adopted: i) BS patients diagnosed as definite or probable p-NBS according to 2014 ICR criteria (5); ii) IFX used in the treatment of patients. The exclusion criteria included: (i) demographic and baseline clinical information on patients or the outcomes were not described clearly; (ii) data on IFX for p-NBS patients could not be extracted; (iii) publication was a conference abstract, letter to editor or reviews; and (iv) studies published in other than English. We recorded basic information, baseline characteristics, intervention and outcomes from each study.

- Quality assessment

We could not use the Newcastle-Ottawa Scale to assess bias risk due to the absence of control groups in the included studies. Instead, we employed a modified version of the Agency for Healthcare Research and Quality's test for bias assessment, with detailed requirements available in Supplementary Table S2.

Data analysis and meta-analysis

Data analyses were done using SPSS 25.0 and R 4.0.2 with the "meta" package. Data are shown as mean ± standard deviation (SD) for normal continuous variables; median and interquartile range (IQR) for non-normal ones; and frequencies and percentages for categorical ones. Continuous variables were compared using Student's t-test or the Wilcoxon Signed Rank Test. All tests were two-sided, with significance at $p<0.05$. For the single-arm cohort studies in this meta-analysis, pooled proportions and 95% confidence intervals (CI) were determined using inverse variance methods and a random-effect model (19). Data normality was checked via Shapiro-Wilk tests before analysis, and the data were logarithmically transformed, if necessary, to enhance normality. Heterogeneity was significant if $I^2>50\%$ or two-sided $p<0.1$.

To reduce the effect of heterogeneity among the included studies, we synthesised the rates of clinical response and MRI improvement at different timepoints during the therapeutic periods. According to the treatment strategy of IFX and the time of assessment in the included articles, we evaluated the efficacy of IFX at 3, 6, and 12 months (corresponding to 12–22, 24–44, and ≥48 weeks).

Results

Case series

- Patients' characteristics

Eleven definite p-NBS patients were enrolled. The mean age at the onset of BS and NBS were 26.2±9.8 and 35.1±8.8 years, respectively. Demographic and clinical characteristics of the patients are available in Table I.

All 11 patients presented parenchymal damages and suffered from multiple lesions, which involved hemisphere (9 of 11, 82%), brainstem (9 of 11, 82%), and spinal cord (4 of 11, 36%). The most common neurological symptom was numbness of extremities, which affected 91% of the patients. Others presented as follows: disturbance of urine (55%), headache (55%), fevers and irritating cough (46% each), dysarthria (36%), conscious disturbance and cognitive dysfunction (36%), psychological and behavioural abnormalities (27%), epilepsy (9%). All patients underwent cerebrospinal fluid (CSF) testing, which revealed that four had elevated pressure, eight had pleocytosis, and nine had increased protein levels. The median Rankin score was 4 (IQR3-5), and all the patients were identified as severe. Neurological magnetic resonance imaging (MRI) examination was performed in all patients and indicated parenchymal lesions. Of all the lesions, the brainstem was involved in 9 patients (9 of 11, 82%), followed by the thalamus, the basal ganglia, the periventricular (3 of 11, 27% each), and the internal capsule (2 of 11, 18%), the temporal lobe and the parietal lobe (1 of 11, 9%). Four patients showed abnormal signals in the spinal cord, including cervical cord involvement in four and thoracic cord involvement in three.

Other BS manifestations involved oral ulcers (n=11), skin lesions (n=7), genital ulcers (n=5), uveitis (n=5), vascular involvement (n=3, both deep venous thrombosis of the lower extremity), intestinal ulcers (n=2), arthritis (n=1).

- Treatment and efficacy assessment

Before IFX, all patients received high doses of GCs and/or immunosuppressants at the initial diagnosis of NBS, but had an inadequate response. Among them, 9 patients received methylprednisolone pulses (0.5~1.0g/d* 3~5d) and then switched to oral prednisone 1 mg/kg/d, two patients received 1 mg/kg/d of prednisone (or equivalent dosage of other corticosteroid) orally in combination with immunosuppressants. IFX was added to these patients (at a dose of 5 mg/kg every 8 weeks following loading doses at weeks 0, 2, and 6). Before starting IFX treatment, routine screening was performed for latent tuberculosis (TB), hepatitis B and C, human immunodeficiency virus, and malignancies. Patients with latent

Table I. Inflixmab therapy in the eleven cases of severe p-NBS from our institution.

			Neurological features				Alteration of clinical manifestations					
Case	sex/ age	Clinical features	Neurological symptoms	Lesions sites	Previous treatment	Background treatment with IFX	Duration of IFX treatment (months)	3m	6m	≥ 12m	MRI outcome	Hamdy and Woldea-manuel simple response score, 2020
1	M/48	O, G, S	numbness of extremities, urinary incontinence, irritating cough	Brainstem, spinal cord	MP pulses GCs CTX	GCs CTX HCQ	6	PR	PR	-	NA	2
2	M/23	O, S	headache, fevers, numbness of extremities, urinary incontinence	Hemisphere, brainstem	MP pulses GCs HCQ THD CTX	GCs CTX	8	PR	PR	-	improved	5
3	M/37	O, G, U	headache, numbness of extremities, visual loss, irritating cough, conscious disturbance and cognitive dysfunction	Hemisphere, brainstem	MP pulses GCs CTX MTX THD	GCs CTX	6	PR	PR	-	improved	5
4	F/38	O, G, S	headache, fevers, numbness of extremities, irritating cough, dysarthria, psychological and behavioral change	Hemisphere, brainstem	MP pulses GCs	GCS CTX MTX	30	PR	CR	CR	clear regression	4
5	M/57	O, U, A	numbness of extremities, dysarthria, irritating cough	Brainstem	MP pulses GC MTX	GCs AZA	32	PR	PR	PR	improved	4
6	M/51	O, V, S, I	psychological and behavioral change, conscious disturbance and cognitive dysfunction, irritating cough	Hemisphere	GCs THD CTX MTX	GCs THD CTX	3	PR	-	-	N/A	2
7	M/31	O, U	fevers, dysarthria, numbness of extremities	Hemisphere, brainstem	GCs CsA	GCs CTX MTX THD COL	31	PR	PR	PR	improved	4
8	M/38	O, G, U	numbness of extremities, urinary incontinence; conscious disturbance and cognitive dysfunction	Hemisphere, brainstem, spinal cord	MP pulses GCs CsA THD	GCs AZA	3	PR	-	-	improved	5
9	F/38	O, V, S, I	numbness of extremities, urinary incontinence	Hemisphere, spinal cord	MP pulses GCs LEF MTX CTX	GCs CTX	20	PR	PR	PR	improved	5
10	M/32	O, G, S, U	headache, fevers, numbness of extremities, urinary incontinence, dysarthria, irritating cough	Hemisphere, brainstem, spinal cord	MP pulses GCs MMF CTX MTX	GCs CTX	8	PR	PR	-	N/A	2
11	M/31	O, S, V	headache, numbness of extremities, urinary incontinence, psychological and behavioral change, conscious disturbance and cognitive dysfunction	Hemisphere, brainstem	MP pulses GCs MTX CTX MMF HCQ	GCs MTX HCQ	4	PR	-*	-	improved	-*

A: arthritis; AZA: azathioprine; CR: complete response; CsA: cyclosporine A; CSF: cerebrospinal fluid; CTX: cyclophosphamide; F: female; G: genital ulcer; GCs: glucocorticoids; HCQ: hydroxychloroquine; I: intestinal ulcers; IFX: infliximab; M: male; MP: methylprednisolone; MMF: mycophenolate mofetil; MTX: methotrexate; N/A: unavailable; NBS: neuro-Behçet's syndrome; NR: no response; O: oral ulcer; PR: partial remission; S: skin lesions; TCZ: tocilizumab; THD: thalidomide; U: uveitis; V: vascular involvement. *Case 11 discontinueed IFX due to acute tuberculosis.

TB infection were administered with tuberculosis prophylaxis (case 8).

The median duration of IFX treatment was 8 (IQR 4–30) months. One patient achieved CR and the other ten patients achieved PR. Radiological lesions disappeared in one patient and alleviated considerably in six (Fig. 1A and 1B). Additionally, in patients with CR and PR, Rankin score decreased from a median of 4 at the initiation of IFX to 2 at the last visit (p=0.0002) (Fig. 1C), CRP dropped from 7.4 (IQR1.9–32.6) mm/h to 1.0 (IQR 0.5–3.4) mm/h, (p=0.05), and ESR declined from 16 (IQR10-22) mm/h to 5 (IQR 1–8) mm/h, (p=0.04). The BDCAF score decreased significantly from a median of 2.5 to 0 at the last visit (p<0.0002) (Fig. 1D). Besides, IFX allowed a significant GCs reduction in the daily dose (of prednisone or equivalents) from 52.1±6.1 mg/day at the initial date to 15.7±3.0 mg/day at the last visit (p=0.0002) (Fig. 1E). Table I shows detailed information about IFX efficiency at each follow-up for 11 NBS patients treated with IFX.

It is noteworthy that case 11 developed acute haematogenous TB four months after initiating IFX, despite having a negative TB screening. The standard short-course anti-TB regimen was initiated, while IFX was stopped

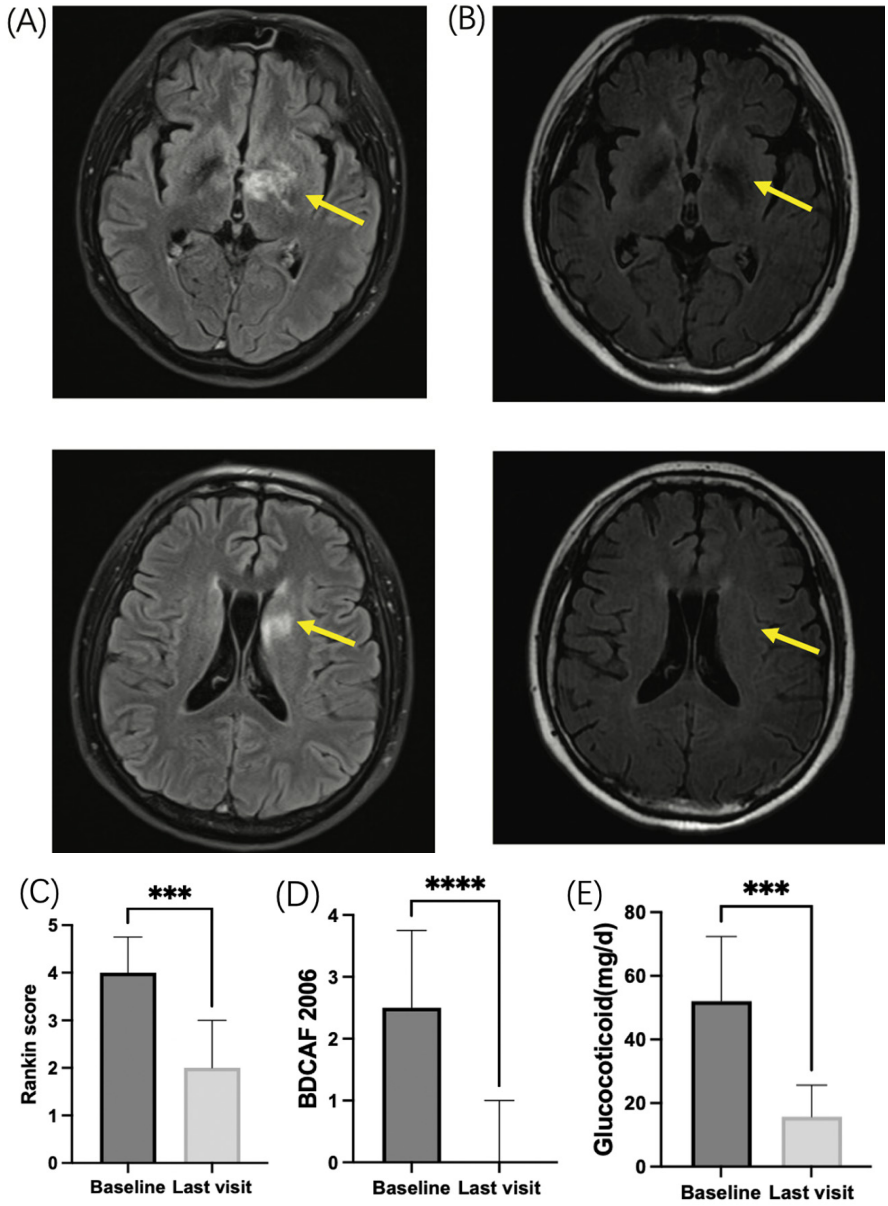

Fig. 1. The outcome of patients with severe and refractory NBS patients following IFX treatment. High-intensity lesions in T2 Flair images at baseline (**A**). The lesions were significantly attenuated after three IFX infusions (**B**). The Rankin score at baseline and the last visit (**C**). The BDCAF score at baseline and the last visit (**D**). Dose of prednisone (mg/day) of patients treated with IFX at baseline and the last visit (**E**).
BDCAF: Behçet's Disease Current Activity Form; NBS: neuro-Behçet's syndrome; IFX: infliximab.

and switched to Interferon-alpha 2a (IFNα2a) later. No other serious adverse effects (AEs) were detected. The rest of the patients with CR and PR remained stable throughout the follow-up period, with no relapse observed.

In addition, we used "Hamdy and Woldeamanuel Simple Response Score, 2020" to score 11 patients in our centre, with a mean score of 3.8±1.3. The specific scores are shown in Table I. It indicated that IFX had a good response in the patients from our institution.

Meta-analysis

- Study selection, characteristics of included studies and quality assessment

In total, 412 articles were retrieved. After eliminating 151 duplicate articles and screening titles and abstracts, 60 full-text studies were examined. Among these, 2 studies lacked sufficient data information, 26 conference abstracts, 7 letters, and 14 case reports were excluded. One retrospective study was omitted due to a lack of precise description regarding types of NBS. Finally, 8 studies involving a total of 77 patients (59 males and 18 females) were identified to perform the meta-analyses by adding the results from our institution. With the exception of one patient classified as probable NBS in the article by Pipitone *et al*. (11), all other patients can be classified as definite NBS based on the 2014 ICR criteria. The pooled efficacy evaluation was presented separately in Table II (6, 7, 9-13). The study selection process is illustrated in Figure 2. In the selected studies from databases, three of the 7 included studies were retrospective, 2 were prospective, and 2 were case series. All five cohort studies were single-armed, with one being a multi-centre study and the rest being single-centre. Six patients received IFX as the first-line therapy due to the severity of their disease, while others were relapsed, refractory, or intolerant to previous conventional therapy before IFX. Twenty-one patients were reported to have received methylprednisolone pulses before IFX treatment. Six patients (7.8%, 6/77) were treated with IFX alone, while 92.2% of patients received IFX in combination with GCs and/or immunosuppressants.

Characteristics of the included studies are summarised in Supplementary Table S3. The risk of bias assessment was listed in Supplementary Table S4. Three of the 7 studies had predetermined protocols. One study had a high risk of attrition bias, and because this study only had three patients, one of them withdrew consent and stopped the study at week 22 even though there had been no acute symptoms after receiving IFX medication. As the included studies were single-arm cohort studies or case series, none of them reported blinding methods. In terms of other aspects, no studies with a high risk of bias were identified.

- Efficacy of IFX in NBS

Follow-up time and duration of IFX treatment for IFX therapeutic response (n=77) ranged from 3 to 104.9 months, with 79.2% (61/77) of patients being followed for more than 12 months. Two patients were reported to have relapsed during treatment, one patient

Table II. Synthesised therapeutic efficacy evaluation of included studies in the meta-analysis and data from PUMCH.

Aspects of therapeutic efficacy evaluation	Time of evaluations	Pooled improvement proportion of clinical symptoms / MRI (%)	Data from PUMCH (%)
Pooled proportion of clinical complete remission (%)	3-months	14.7	0
	6-months	28.7	12.5
	≥12 months	54.4	25.0
Pooled proportion of clinical partial remission (%)	3-months	97.0	100
	6-months	89.6	100
	≥12 months	100	100
Pooled proportion of MRI improvement (%)	3-months	100	100
	6-12 months	89.1	100
	≥12 months	99.5	100

Data from PUMCH were carried out in our institution and were not published before.

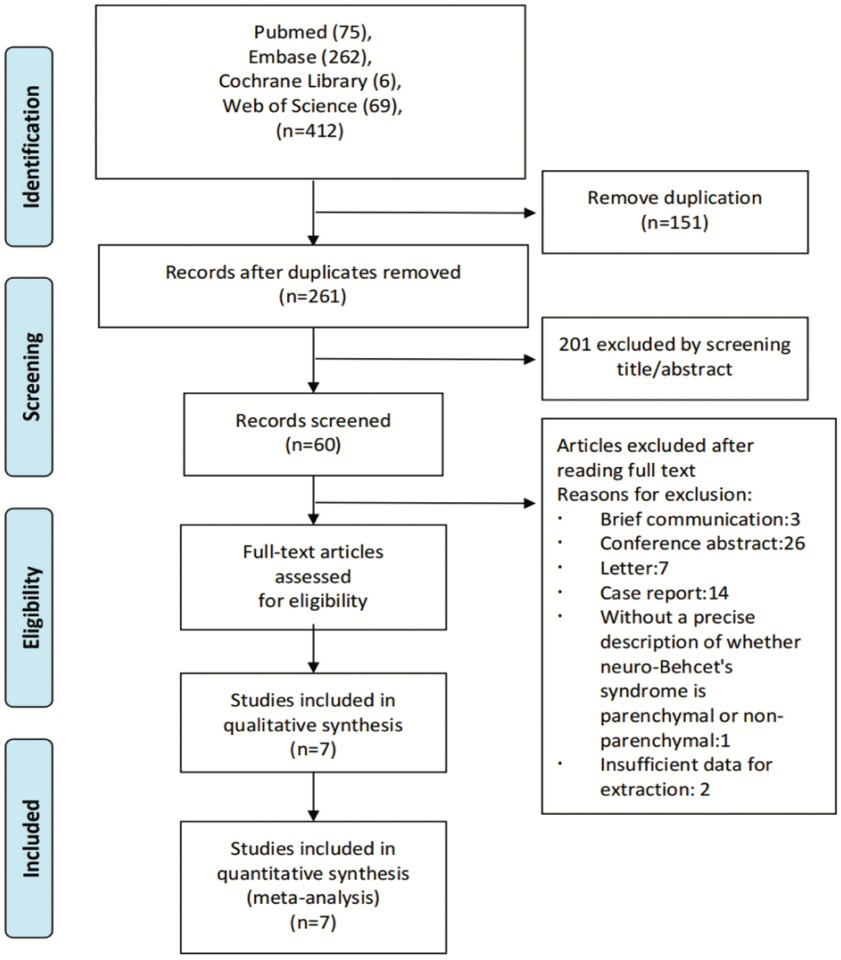

Fig. 2. The flow diagram of this meta-analysis.

relapsed in the 11th month of IFX treatment and achieved complete remission after switching to tocilizumab. Two patients relapsed after discontinuing IFX for 2 and 12 months, respectively.

- Clinical response (complete remission)

Results of pooled proportions of clinical complete remission were shown in Figure 3A, 3B and 3C. Four, five and six studies with 19, 17, and 57 patients each were conducted to assess the clinical complete remission rate of IFX for NBS at Month 3, Month 6, Month 12. Clinical complete remission was achieved in 14.7% (95%CI 0.00-83.5%) of patients at Month 3, 28.7% (95% CI 0.00-86.7%) of patients at Month 6, 54.4% (95%CI 13.9-92.3%) at Month 12. The level of heterogeneity was moderate to high, with I^2 values of 80%, 63%, and 87% observed at Month 3, Month 6, and Month 12, respectively, necessitating a random-effect model.

- Clinical response (partial remission)

Results of pooled proportions of clinical partial remission were shown in Figure 3D, 3E and 3F. Four, five, and six studies with 19, 17, and 57 patients each were conducted to assess the clinical partial remission rate of IFX for NBS at Month 3, Month 6, Month 12. Clinical partial remission was achieved in 97.0% (95%CI 61.9-100%) of patients at Months 3, 89.6% (95%CI 45.9-100%) of patients at Months 6, 100.0% (95%CI 96.0-100%) at Months 12. Heterogeneity was not significant between studies on any phase of partial remission (I^2=0-46%).

- MRI improvement

Results of pooled proportions of MRI improvement were shown in Figure 4. Three, four, and six studies containing 9, 7, and 54 patients were conducted to assess the MRI improvement rate of IFX for NBS at Month 3, Month 6, Month 12. MRI improvement was achieved in 100.0% (95%CI 89.7-100%) of patients at Month 3, 89.1% (95% CI 26.3-100%) of patients at Month 6, 99.5% (95% CI 96.0-100%) at Month 12. The level of heterogeneity ranged from low to moderate, with I^2 values of 0%, 65%, and 0% observed at Month 3, Month 6, and Month 12, respectively.

Safety of IFX in the treatment of neuro-Behçet's syndrome

A total of 8 studies with more than 16 patients reported safety information. Among them, 7 patients (9%, n=77) experienced severe AEs. Supplemen-

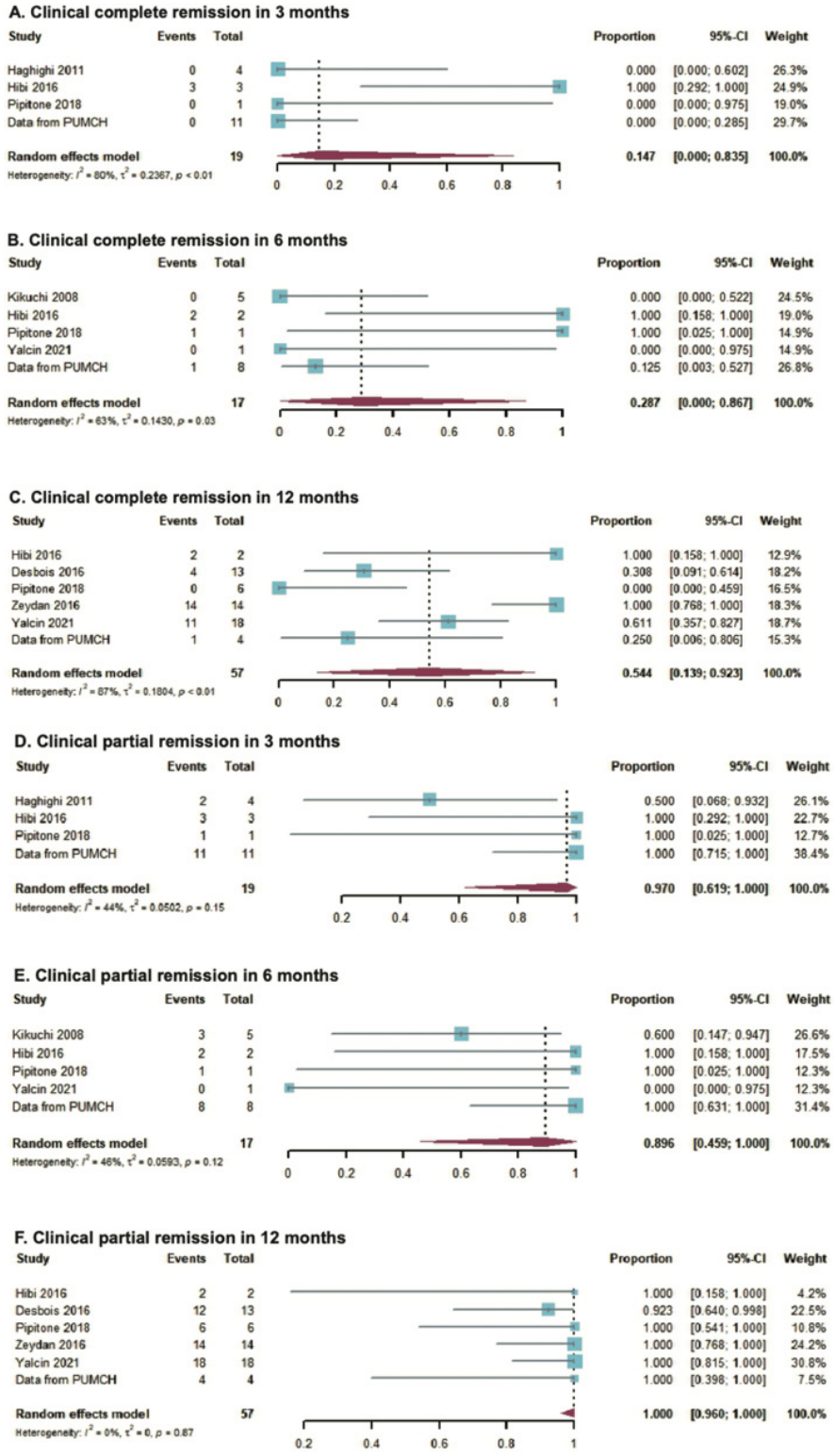

Fig. 3. Results of pooled proportions of clinical complete remission in patients treated by IFX agents in 3 months (**A**), 6 months (**B**), and 12 months (**C**). Results of pooled proportions of clinical partial remission in patients treated by IFX agents in 3 months (**D**), 6 months (**E**), and 12 months (**F**). Data from PUMCH was carried out in our institution and was not published before.

tary Table S5 summarises the detailed information on AEs reported by studies connected to IFX used in treating NBS. Serious AEs included pneumonia (n=2), varicella zoster infection (n=1), heart failure (n=1), behavioural disorder (n=1), acute TB (n=1), and allergic reaction (n=1). The latter four patients eventually discontinued treatment due to the severe AEs (7, 12). There were no AE-related deaths.

Discussion

We conducted a retrospective study and a meta-analysis to summarise the proportions of clinical response and MRI improvement at multiple follow-up time points in p-NBS patients treated with IFX therapy, as well as the incidence of overall AEs. Our findings suggested that IFX therapy has a promising effect in improving the clinical symptoms of p-NBS patients, with a partial resolution of radiological lesions. Furthermore, nearly half of the patients achieved complete remission of neurological symptoms at 12 months. Our time-course analysis indicated that IFX exerted its effect within 3 months and was sustained at 6 and 12 months. A remarkable steroid-sparing effect and a significantly decreased ranking score were also observed in our cohort. These results support the use of IFX in p-NBS treatment.

NBS is one of the most serious causes of long-term mortality in BS, and the pathogenesis of NBS is not fully understood. Recent studies indicated that TNF-α is a critical proinflammatory cytokine in p-NBS, mainly produced by macrophages, NK cells, and T cells, which contributes to neutrophil activation, causing chronic vascular inflammation and multi-organ tissue damage (20). Given its pivotal role, anti-TNF-α agents act more precisely than conventional immunosuppressants and could be a better solution for severe and (or) refractory p-NBS.

To date, only three studies have reported a cohort of more than ten NBS patients on IFX, and our data included eleven patients with detailed records, which greatly strengthens this conclusion. It is also the largest study in China on this issue. The recent meta-analysis of 21 studies with 64 NBS patients showed a pooled efficacy of 94% (95% CI 88–93%) for IFX in treating NBS (16). Focusing on p-NBS, a specific subtype with worse outcomes, our study included the report of case series from our institution and additionally performed a comprehensive meta-analysis to depict

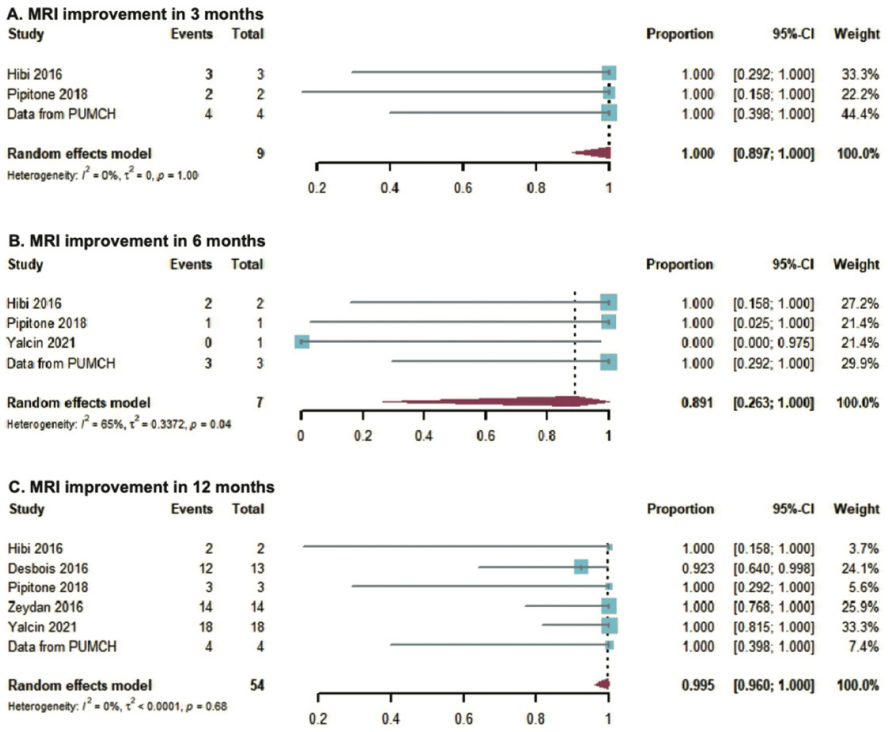

Fig. 4. Results of pooled proportions of MRI improvement in patients treated by IFX agents in 3 months (**A**), 6 months (**B**), and 12 months (**C**).
Data from PUMCH was carried out in our institution and was not published before.

a more accurate picture of the IFX effect. Furthermore, we evaluated the efficacy of IFX every 3 months, both clinically and radiologically, and concluded that IFX was clinically effective within 3 months (97%) and maintained the desired therapeutic effect at 6 months (89.6%) and 12 months (100%). Regarding radiological changes, the improvement rate was 100% at 3 months, 89.1% at 6 months, and 99.5% at 12 months. Due to the variable inclusion of studies at different monthly assessment points, there was a slight decrease in the clinical and MRI partial remission rate at month 6 compared to month 3. However, a consistently high pooled efficacy of approximately 90% for IFX confirmed its effectiveness in treating p-NBS. It is thought-provoking that the pooled efficacy in p-NBS was remarkably high. One of the reasons is that, unlike intestinal BS (21), there is no clear and distinct standard for evaluating the drug response in NBS. Although the "Hamdy and Woldeamanuel neuro- Behçet's simple response score, 2020" has been introduced to assess the response to treatment, it only comprises a rough score and simple merging of clinical, radiologic, and CSF changes without a quantified description of improvement. This highlights the need for a standardised and accurate evaluation process in NBS treatment.

Anti-TNF-α biologics are recommended as first-line treatment for severe p-NBS or in refractory cases, but inadequate responses have still been observed in some patients. Our group has previously reported that IFNα2a (22), interleukin (IL)-6 receptor antagonist tocilizumab (TCZ) (23), and IL-17 blocker secukinumab (SEC) (24) had a favourable effect, providing more options for refractory p-NBS patients. Based on our analysis, it is recommended to set three months as the time point for IFX treatment in p-NBS. If no significant improvement is observed within 3 months, it is worth considering a new treatment regimen such as IFNα2a, TCZ, and SEC.

AEs associated with IFX treatment deserve close supervision. Seven patients (7/77, 9.1%) experienced serious AEs, including acute TB in one patient, and stopped IFX treatment. Anti-TNF-α antibodies may increase the risk of TB infection and reactivation of latent TB and HBV (25). Given the high incidence of TB and HBV infection in China, prophylactic treatment is required before anti-TNF-α antibody administration in BS patients with latent TB. However, serious events may still occur.

This study has some limitations. Firstly, there are no randomised control trials (RCT) in NBS, and the length of follow-up duration varied widely across the included studies, and only 4 patients from our institution reached 12 months of follow-up, which might cause potential bias of relapse due to short-term follow-up. Besides, the efficacy of IFX was evaluated in a relatively small population of 77 patients, making it susceptible to highly variable outcomes. Additionally, there might be a publication bias as all the articles reported positive results of their clinical trials, and this could overestimate the efficacy of IFX in NBS. To address these limitations, we defined specific inclusion and outcome criteria and only included studies with clear evaluation times.

In conclusion, our study provides a valuable reference on the efficacy and safety of IFX in treating p-NBS. Our results indicated that IFX was a promising therapy with good efficacy and low AEs for p-NBS to improve their prognosis. Also, NBS patients should be thoroughly evaluated after three months of IFX therapy to adjust subsequent treatment. Prevention of relapse and control of disease progression are crucial goals for p-NBS, and more well-designed, large-scale RCTs are needed to validate our findings.

Acknowledgments

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