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Effectiveness and safety of low-dose interferon alpha-2a treatment in Behçet's Syndrome with refractory vascular or neurological involvement: a case series

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Abstract

Objective: The aim of this study was to evaluate the effectiveness and safety of low-dose interferon alpha-2a (IFNα2a) in Behçet's syndrome (BS) patients with refractory vascular/cardiac or neurological involvement.

Methods: In this retrospective cohort study, we consecutively included 25 BS patients with refractory vascular/cardiac ($n = 16$) or neurological involvement ($n = 9$) who received IFNα2a treatment in our center between June 2018 and September 2021. The low-dose IFNα2a (3 million IU, every other day) was used as an add-on treatment with the continuation of glucocorticoids (GCs) and immunosuppressants.

Results: In total, 25 patients (20 males, 5 females) with a mean age of 31.92 ± 9.25 years were included. IFNα2a was administered for BS patients with refractory vascular/cardiac involvement ($n = 16$) and neurological involvement ($n = 9$). Before the initiation of IFNα2a, patients had insufficient response or intolerance to conventional therapies. After a median follow-up of 23 [interquartile range (IQR), 11–30] months, all patients achieved clinical improvement. The Behçet's disease Current Activity Form (BDCAF) score improved significantly (5 *versus* 0, median, $p < 0.0001$). BS Overall Damage Index (BODI) and vasculitis damage index (VDI) remain stable ($p > 0.05$). Decrease in erythrocyte sedimentation rate [ESR; 24 (IQR, 12–43.5) *versus* 5 (IQR, 2.75–10.5) mm/h, $p = 0.0001$] and C-reactive protein [CRP; 6.64 (IQR, 3.67–19.82) *versus* 1.24 (IQR, 0.24–3.12) mg/liter, $p < 0.005$] was achieved effectively. The median GCs dosage tapered from 26.25 (IQR, 11.88–41.25) to 10.00 (IQR, 7.50–10.63) mg/d, $p < 0.0001$. Immunosuppressants were also reduced in number ($p < 0.005$). No serious adverse events were observed during follow-up.

Conclusion: Our study suggests that low-dose IFNα2a, combined with GCs and immunosuppressants, is well-tolerated and effective for BS patients with refractory vascular/cardiac or neurological involvement and has a steroid- and immunosuppressant-sparing effect.

Keywords: Behçet's syndrome, clinical effectiveness, interferon α2a, neurological involvement, refractory vascular/cardiac involvement

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Introduction

Behçet's syndrome (BS) is a chronic and relapsing systemic vasculitis characterized by mucocutaneous lesions and multi-organ involvement, with different phenotypic clusters.[1] For severe/refractory BS with ocular, vascular, neurological, or gastrointestinal involvement, monoclonal anti-tumor necrosis factor-alpha (TNF-α) antibodies are recommended according to the 2018 European League Against Rheumatism (EULAR)

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management guidelines.[2] However, the potential risk of anti-TNF-α inhibitors, particularly monoclonal anti-TNF-α antibodies, in the reactivation of latent tuberculosis (TB) and hepatitis B virus (HBV) posed a concern in TB/HBV endemic countries, such as China.[3,4] Therefore, an unmet need exists for additional therapeutics. Human interferon alpha-2a (IFNα2a) has been shown to have comparable beneficial effects and safety profile as monoclonal anti-TNF-α antibodies on BS uveitis (BU) and is superior to conventional therapies in refractory BU.[2,5] However, to date, only a few case reports or series have shown a favorable effect of IFNα2a in the treatment of BS patients with other organ involvement, for example, skin, mucosal,[6,7] deep vein thrombosis,[8] and neurological manifestations.[9] There is no consensus on the dose of IFNα2a in BS patients. The available data suggest the increased potential risk of adverse effects of high-dose IFNα2a in combination with immunosuppressive therapy, for example, infection and hepatic impairment. Our team first reported the effectiveness of low-dose IFNα2a combined with glucocorticoids (GCs) and multiple immunosuppressants in Chinese refractory BU.[10] Here, we report the largest cohort of the effectiveness and safety of low-dose recombinant human IFNα2a as an add-on treatment in a series of BS patients with refractory neurological or vascular/cardiac involvement, and first reported that in the artery and cardiac involvement, in the Chinese Han Population.

Patients and methods

Study design and patients

We consecutively included 25 BS patients with refractory vascular/cardiac involvement or neurological involvement. These patients received IFNα2a treatment at Peking Union Medical College Hospital (PUMCH) between June 2018 and September 2021, and they were evaluated using a retrospective chart review. All patients fulfilled the 2014 International Criteria for Behçet's disease (ICBD).[11] Diagnosis of BS with vascular/cardiac involvement (VBS) was established by consensus determination of rheumatologists, cardiologists, and cardiac/vascular surgeons based on clinical manifestations and imaging findings (Doppler ultrasound, echocardiography, and computed tomography angiography). Diagnosis of neurological involvement of BS (NBS) was established based on the neurological symptoms, cerebrospinal fluid analysis, and neuroradiological examinations, according to the 2014 International Consensus Recommendation criteria on NBS.[12] Patients with VBS or NBS refractory or intolerance to conventional therapies were eligible for inclusion in the study. Patients were regarded as refractory cases if they did not respond adequately to conventional BS treatment for at least 3 months. Patients' intolerance to conventional therapies was defined as the presence of any steroid or immunosuppressant-related side effects or contraindications.

The main exclusion criteria were as follows: neurological manifestations not differentiated from other rheumatic diseases, infection/encephalitis/myelitis, brain/spinal cord tumor, vascular disorders, syphilis, multiple sclerosis, or psychiatric disease; cardiovascular manifestations not differentiated from Takayasu's arteritis, Buerger's disease, or arteriosclerotic aneurysm. Other exclusion criteria were severe liver and kidney insufficiency, current active TB, active hepatitis B or C, persistent or severe bacterial or viral infections, malignancy within the last 5 years, or pregnancy. Patients with active TB were excluded unless they completed treatment for TB supervised by infectious disease specialists; patients with evidence of latent TB completed at least 1 month of TB prophylaxis before receiving IFNα2a.

IFNα2a was administered at a dose of 3.0 million IU (MIU) subcutaneously every other day for 3–6 months, and further tapering was tailored to individual immunosuppression needs. Concurrent therapies included maintained or decreased GCs and immunosuppressants. The immunosuppressants included cyclophosphamide (100–150 mg/day), cyclosporin A (150–200 mg/day), mycophenolate mofetil (1–1.5 g/day), azathioprine (AZA; 100 mg/day), methotrexate (10 mg/week), and leflunomide (20 mg/day).

The following data were collected and analyzed: demographic data, clinical manifestations, and medical history. Concurrent therapies, laboratory tests, and adverse events were recorded at each visit. Radiological examinations were repeated every 3–6 months during follow-up.

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of PUMCH (S-443).

Written informed consent for collecting and using data, examinations, treatments, and publication was obtained from all patients following the IRB's requirements. The patient's records and information were anonymized and deidentified before analysis.

Outcome assessment

The primary aim was to evaluate the response of IFNα2a treatment in refractory BS patients. The clinical outcome was defined as follows:[13] (1) improved: the resolution of BS-related manifestations, improvement of radiological abnormalities related to VBS or NBS, and no newly onset of imaging findings up to the time of evaluation compared to baseline at 12–24 weeks after IFNα2a treatment; (2) unchanged or worsened: the BS-related clinical manifestations or inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], or imaging findings persisted or worsened compared to baseline at 12–24 weeks after IFNα2a treatment. BS disease activity was assessed using Behçet's Disease Current Activity Form (BDCAF) 2006 (http://www.behcet.ws/pdf/BehcetsDiseaseActivityForm.pdf). Damage in BS patients was assessed by BS Overall Damage Index (BODI)[14] and vasculitis damage index (VDI).[15] A modified Rankin score was used to assess the disability status of patients with NBS in this study. Severe NBS was defined as Rankin score $\geqslant 3$.[16] Radiological improvements were defined by the disappearing or attenuation of radiological abnormalities related to NBS or VBS, which were confirmed independently by two researchers. Secondary outcomes included GCs and immunosuppressant-sparing effects and safety of IFNα2a.

Statistical analysis

A sample size of nine patients was calculated to achieve 80% power at a 5% significance level, a 10% attrition rate, for a two-sided McNemar test (PASS 15). We assumed that the patients who had an inadequate response to GCs and immunosuppressants were predicted to have a 70% clinical response rate in combination with IFNα 2A therapy according to literature and our previous experience.[8,10]

Qualitative variables were represented as frequencies and percentages. Data with Gaussian distribution were expressed as mean value ± standard deviation. Data with non-Gaussian distribution were described as the median and interquartile range (IQR). The significance was estimated by the Student's *t*-test or Wilcoxon test. A two-sided with a *p*-value less than 0.05 was considered a statistically significant difference. SPSS version 22.0 (IBM Inc., Armonk, USA) was used to perform the statistical analyses.

Results

Demographic features

In total, 25 BS patients (20 males and 5 females) with a mean age of 31.92 ± 9.25 years were included. The median time interval between BS diagnosis and IFNα2a administration was 72 (IQR, 36–120) months. Demographic features are demonstrated in Supplementary Table 1.

Clinical manifestations

The main clinical features and outcomes of patients with VBS ($n=16$) and NBS ($n=9$) are shown in Tables 1 and 2. Of the 16 VBS patients included, 13 patients (81.3%) had venous lesions (including 9 cases with multiple thrombosis), and 8 patients (50%) had arterial lesions (including multiple arterial lesions in 4 patients). 5 cases (31.3%) had both veins and arteries lesions. In addition, 3 patients had cardiac involvement, including ventricular aneurysm of the left apex and right ventricular occupation ($n=2$), and aortic artery root dilation with severe aortic valve regurgitation (AVR) who experienced perivalvular leakage (PVL) after cardiac operations two times ($n=1$).

All nine NBS patients had parenchymal involvement. The most commonly involved sites were brainstem ($n=6$), followed by spinal cord involvement ($n=4$) and hemisphere ($n=4$). Six cases suffered from multiple neurological lesions. Three patients also presented with cranial venous sinus thrombosis.

Previous treatments and associated adverse events

All patients had been treated with systemic GCs (100%) and immunosuppressants (96%), including cyclophosphamide ($n=21$), mycophenolate mofetil ($n=5$), AZA ($n=4$), leflunomide ($n=4$), cyclosporin A ($n=3$), methotrexate ($n=2$), and

Table 1. Follow-up data of 16 BS patients with vascular/cardiac involvement treated with IFNα2a.

Case	Gender/ age	Disease duration (months)	Clinical manifestations	Previous treatment	Concurrent treatment	Follow-up (months)	Outcome	Radiological change
1	M/30	75	O, U, S, V (stenosis/occlusion of multiple arteries, lower limb DVT with PTS)	GC, CsA, CTX	GC, CsA, CTX	37	Improved	Improved
2	M/29	125	O, G, S, V [multiple VT (SVC, IVC, lower limb)]	GC, CTX	GC	41	Improved	Improved
3	M/39	13	O, V [PVL (twice), pseudoaneurysm of aortic root]	GC, CTX	GC, CTX	15	Improved	Stable
4	F/30	40	O, U, S, V (stenosis/occlusion of multiple arteries)	GC, THD, COL, CTX	GC, THD, COL	24	Improved	Improved
5	M/23	124	O, G, V [multiple VT (right ventricular, IVC, lower limb)]	GC, CTX, THD	GC	23	Improved	Stable
6	M/36	19	O, U (stable), V (aneurysm, lower limb DVT)	GC, CTX, AZA	GC, CTX, AZA	11	Improved	Improved
7	M/19	80	O, G, S, V (lower limb DVT)	GC, THD, LEF, COL	GC, COL	30	Improved	Stable
8	M/26	86	O, G, S, V [multiple VT (IVC, lower limb with PTS)]	GC, CTX, MTX, LEF, THD, COL	GC, LEF, THD, COL	37	Improved	Stable
9	M/25	10	O, G, S, N, V (multiple stenosis of pulmonary arteries, left VA of apex)	GC, CTX	GC, THD, CTX	7	Improved	/
10	F/22	52	O, G, S, V [multiple VT (IVC and renal vein)]	GC, CTX, MMF	GC, MMF, COL	27	Improved	Improved
11	M/35	100	O, U (stable), S, V (multiple VT and stenosis of lower limbs with PTS)	GC, THD, CTX, AZA, TAC	GC, THD	9	Improved	Improved
12	F/46	364	O, G, S, V [multiple VT (jugular vein, lower limb) and PTE]	GC, CTX, COL, T2, LEF, MMF, TCZ	GC, CTX, MMF, COL	23	Improved	Improved
13	M/33	20	O, G, S, V (lower limb DVT and PTE)	GC, CTX, COL, T2	GC, CTX, LEF, COL	10	Improved	Stable
14	M/32	128	O, G, S, V [multiple VT (brain and lower limb)]	GC, CTX, THD	GC, CTX, THD, COL	10	Improved	Stable
15	M/21	40	O, S, V [multiple VT (lower limb)]	GC, T2, MMF, HCQ, THD, COL	GC, MMF, COL, THD	19	Improved	Stable
16	M/26	132	O, G, S, V (lower limb DVT with PTS)	GC, THD, CTX, CsA	GC, LEF, COL	6	Improved	/

ADA, adalimumab; AZA, azathioprine; COL, colchicine; CsA, cyclosporin A; CTX, cyclophosphamide; DVT, deep venous thrombosis; EN, erythema nodosum; G, genital aphthosis; GC, glucocorticoids; HCQ, hydroxychloroquine; IVC, inferior vena cava; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; N/A, unavailable; O, oral aphthosis; PTE, pulmonary thromboembolism; PTS, post-thrombotic syndrome; PVL, postoperative perivalvular leakage; S, skin involvement; SASP, sulfasalazine; SVC, superior vena cava; T2, tripterygium glycoside; TAC, tacrolimus; TCZ, tocilizumab; THD, thalidomide; U, uveitis; V, vascular involvement; VA, ventricular aneurysm; VT, venous thrombosis.

Table 2. Follow-up data of nine BS patients with neurological involvement treated with IFNα2a.

Case	Gender/ age	Disease duration (months)	Clinical features	Previous treatment	Concurrent treatment	The change of Rankin score	Follow-up (months)	Outcome	Radiological change
1	F/34	334	O, G, U, S, N (brainstem and CVST)	GC, HCQ, MMF	GC, HCQ, MMF	2→0	37	Improved	Clear regression
2	M/42	64	O, G, S, N (spinal cord)	GC, CTX, MTX, COL, TCZ	GC, CTX, MTX, COL, MMF	5→4	36	Improved	Improved
3	M/41	136	O, U, N (brainstem)	GC, TOF, CTX, COL	GC, CTX	1→0	30	Improved	Improved
4	M/57	124	O, N (hemicerebrum, brainstem, spinal cord)	Pulse GC therapy	GC, MTX	4→2	23	Improved	Improved
5	M/41	49	O, G, N (brainstem, spinal cord)	Pulse GC therapy, CTX, THD	GC, CTX, THD	5→4	8	Improved	/
6	M/21	19	O, G, S, N (brainstem, spinal cord)	GC, AZA, CTX, THD, LEF	GC, COL, LEF, CTX	2→1	24	Improved	Clear regression
7	M/32	124	O, V, N (hemicerebrum, diencephalon)	GC, CTX	GC, CTX	1→0	25	Improved	Improved
8	F/37	76	O, G, U, N (hemicerebrum, brainstem, CVST)	GC, CTX, MMF, HCQ	GC, MMF	1→0	21	Improved	Improved
9	M /44	48	O, G, A, S, U (stable), N (hemicerebrum, CVST)	GC, THD, HCQ, AZA, CTX, CsA	GC, THD, AZA	4→2	31	Improved	/

A, arthritis; AZA, azathioprine; COL, colchicine; CsA, cyclosporin A; CTX, cyclophosphamide; CVST, cranial venous sinus thrombosis; G, genital aphthosis; GC, glucocorticoids; HCQ, hydroxychloroquine; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; N, neurological involvement; N/A, unavailable; O, oral aphthosis; S, skin involvement; TOF, tofacitinib; TCZ, tocilizumab; THD, thalidomide; U, uveitis; V, vascular involvement.

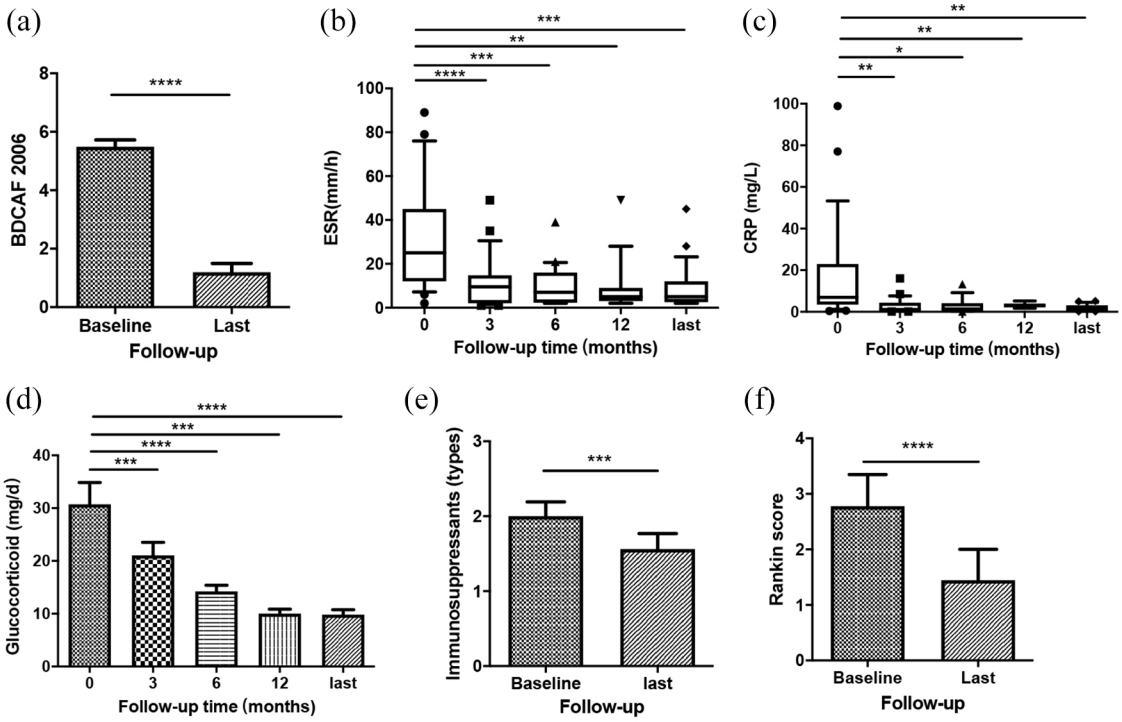

Figure 1. Effectiveness of IFNα2a in patients with refractory BS. (a) The BDCAF score of patients treated with IFNα2a at baseline and the last visit ($n = 25$). Change in (b) ESR and (c) CRP of patients treated with IFNα2a during the time of follow-up. (d) Dose of prednisone (mg/day) of patients treated with IFNα2a at baseline and the last visit. (e) Types of immunosuppressants of patients treated with IFNα2a at baseline and the last visit. (f) The change of Rankin score of patients with NBS at the initiation and the last treatment visit with IFNα2a. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

tacrolimus ($n = 1$), before IFNa2α therapy. Meanwhile, 76% of patients had received two or more immunosuppressants. Adverse events related to previous treatments included hepatic impairment (12%), peripheral neuropathy (4%), drug allergy (4%), and infection (4%). Two patients (including one NBS and one VBS) had received short-term tocilizumab and responded well, but stopped due to economic burden and active pulmonary TB.

Concomitant medical conditions included TB ($n = 4$) and chronic HBV infection ($n = 2$). Active pulmonary TB ($n = 2$), latent TB ($n = 1$), and previous history of TB ($n = 1$) were recorded. The two patients with active pulmonary TB had received standard anti-TB therapy before IFNα2a treatment. The one patient with latent TB had prophylaxis of isoniazid. The two patients with chronic HBV infection were treated with antiviral therapy before IFNα2a treatment and had undetectable HBV-DNA at the screening visit.

Outcomes

After a median follow-up duration of 23 (IQR, 11–30) months, most patients (96%) achieved improvement with IFNα2a treatment. The overall BDCAF score improved significantly [baseline: 5 (IQR, 5–7) *versus* last visit: 0 (IQR, 0–3), $p < 0.0001$] [Figure 1(a)]. The BODI (baseline: 5.16 ± 2.06 *versus* last visit: 5.20 ± 2.04, $p > 0.05$) and VDI (baseline: 3.32 ± 1.07 *versus* last visit: 3.36 ± 1.04, $p > 0.05$) scores remained stable, indicating no accumulation of damage from recurrent flares or treatment was shown. Significant decreases of the level of inflammatory markers were achieved: ESR [baseline: 24 (IQR, 12.00–43.50) mm/h *versus* last visit: 5 (IQR, 2.75–10.50) mm/h, $p = 0.0001$] and CRP [baseline: 6.64 (IQR, 3.67–19.82) mg/liter *versus* last visit: 1.24 (IQR, 0.24–3.12) mg/liter, $p < 0.005$] [Figure 1(b) and (c)]. Moreover, the median GCs dosage of prednisone (or equivalent) was tapered [baseline: 26.25 (IQR, 11.88–41.25) mg/d *versus* last visit: 10.00 (IQR, 7.50–10.63) mg/d, $p < 0.0001$]

[Figure 1(d)]. Meanwhile, the immunosuppressant dosage was tapered in all 25 patients, and the types of immunosuppressants/immunomodulators decreased from 2 (range 1–3) to 1 (range 1–2) [$p < 0.001$, Figure 1(e)]. During the overall follow-up period, nine patients (36%) maintained 3 MIU of IFNα2a every other day with successfully controlled disease activity and no relapse observed. However, 11 patients (44%) successfully reduced their IFNα2a dosage to 3 MIU thrice or twice weekly and IFNα2a was withdrawn in 5 patients (20%). No increase in the dose of IFNα2a was required in patients during the follow-up period.

Vascular/cardiac involvement. During the median follow-up of 21 (IQR, 10–27.75) months, the clinical symptoms improved in all the 16 VBS patients, with inflammatory markers (ESR and CRP) remaining at a low level. Radiological improvement ($n = 7$) and stable ($n = 7$) of artery lesions and thrombosis were demonstrated in VBS patients during follow-up. One patient showed preexisting deep venous thrombosis (DVT) without developing new vascular lesions (Table 1, Case 7). One patient with severe AVR had failed conventional therapy and developed postoperative PVL two times. He underwent the third cardiac operation with IFNα2a treatment and achieved event-free during the follow-up of 15 months. Meanwhile, he achieved a significantly tapered GCs dose (baseline: 70 mg/d *versus* last visit: 15 mg/d). The BDCAF scores improved significantly in 16 patients (baseline: 5.50 ± 1.15 *versus* last visit: 1.31 ± 1.54, $p < 0.001$). No new onset of thromboses or pseudoaneurysms was observed during follow-up.

Neurological involvement. After a median follow-up of 25 (IQR, 23–31) months, all nine NBS patients achieved clinical and radiological improvements. The lesions disappeared in two patients and attenuated in the rest patients on follow-up MRI (Table 2). The BDCAF score in NBS patients decreased significantly (baseline: 5.44 ± 1.33 *versus* last visit: 1.00 ± 1.50, $p < 0.001$). The Rankin score significantly decreased from 2.78 ± 1.72 to 1.44 ± 1.67, $p < 0.0001$ [Figure 1(f)].

Safety

No serious adverse effects were reported. Four patients (16%) experienced flu-like syndrome but were soon well controlled. Mild/moderate leukocytopenia was observed in three cases (12%). Elevation of serum transaminase and creatine was not observed in this cohort.

Discussion

This study suggested that IFNα2a, combined with GCs and immunosuppressants, produced significant and clinically meaningful improvements in BS patients with refractory vascular/cardiac or neurological involvement, with a sustained benefit over follow-up periods. For the first time, IFNα2a has shown efficacy in treating BS patients with arterial and cardiac involvement. We also introduced BDCAF and VDI/BODI to assess both disease activity and disease/treatment-related chronic damage for the effectiveness of IFNα2a in BS patients. We showed that IFNα2a is effective and well-tolerated, with favorable steroid- and immunosuppressant-sparing effects.

BS shares common features with autoinflammatory and autoimmune diseases, characterized by excessively activated innate immunity, overproduction of proinflammatory cytokines, and skewed Th1 and Th17 cell activation.[17] IFNα2a treatment suppresses inflammation in BS through multiple immune pathways. IFNα2a regulated T cell subsets by increasing Treg cells and inhibiting Th17 cells in the peripheral blood.[18] Natural killer (NK) and gamma delta (γδ) T cells decreased significantly under treatment with IFNα2a.[19] Furthermore, IFNα2a could reduce reactive oxygen species production and phagocytosis of neutrophils.[20] IFNα2a inhibited the expression of Toll-like receptors on $CD4^+$ T cells and monocytes and attenuated innate immune response.[21]

There is no consensus on the dosage and duration of IFNα2a in BS patients. The reported initial dosage of IFNα2a in BS ranges from 3 to 6 MIU daily to 3 MIU every other day.[6–10,21–23] Generally, in BU patients, a higher initial dosage of IFNα2a was administrated and further tapered during the disease achieved remission. In most cases, especially in BU patients, IFNα2a was given only with GCs, without continuation of immunosuppressants. Our group previously reported the first study of the effectiveness and safety of IFNα2a as an add-on treatment for refractory BU by combining IFNα2a with GCs plus multiple immunosuppressants, with promising efficacy and a favorable safety profile of no severe adverse effects at a low initial dose of 3 MIU daily of IFNα2a.[10]

The dose of IFNα2a was successfully tapered or discontinued during follow-up. However, the BU patients recruited in that study had no other major organ involvement. Our current study further explored the application of IFNα2 in BS patients with vascular/cardiac or neurological involvement, who generally received more aggressive immunosuppressants than BU patients. Therefore, based on literature and our experience, we chose a conservative dosing strategy with the initial dose of 3 MIU IFNα2a every other day, combined with GCs and immunosuppressants, as an add-on treatment for these refractory BS patients. Our results showed a favorable effectiveness rate and similar safety profile to the previous study in the conservative dosing strategy.

Vascular/cardiac involvement in BS profoundly affects morbidity and mortality.[24] Only one study described the application of IFNα in VBS. This report showed that IFNα-treated BS patients with deep vein thrombosis had a higher recanalization rate (86% *versus* 45%) and a lower relapse rate (12% *versus* 45%) compared with AZA[8] Our study included venous, arterial lesions, and cardiac involvement in VBS, and is the first study to report the effectiveness of IFNα2a in BS patients with arterial aneurysm and cardiac involvement, suggesting that IFNα may be a promising therapeutic agent for various types of VBS.

NBS is a potentially life-threatening complication of BS associated with severe disability.[25] Our previous study showed a mortality rate of 11.1% for p-NBS.[26] The international consensus recommendations suggested the application of IFNα in NBS patients with refractory to or intolerance to immunosuppressants.[12] However, only a few case reports have shown a favorable effect of IFNα in NBS, with the variation of initial dose ranging from 3 MIU daily to 3–10 MIU every other day (supplementary table 2), making it difficult to evaluate in combination.[26–31] Our study is the largest cohort to date, elucidating the clinical and radiological promising effect of IFNα2a in NBS patients. Using low doses of IFNα2a, a lower incidence of adverse effects was observed. Meanwhile, their remission rates and sparing effects of steroids and immunosuppressants remained stable. This study also demonstrated the improvement of disability status in NBS by Rankin score.[32]

Evidence has shown the potential link between the use of anti-TNF-α antibodies and the increased risk of reactivation of latent TB and HBV.[3,4,33] China ranks in the top countries with a high incidence of TB and HBV infection.[34] In BS patients with latent TB, prophylaxis treatment is required prior to anti-TNF-α antibodies administration, which poses concerns to the risk of its adverse effects (e.g. hepatic impairment) in the combination of multiple immunosuppressants. To date, IFNα has been used for decades without evidence of increasing the risk of latent TB reactivation. Meanwhile, IFNα has been widely used to treat HBV infection.[35] Therefore, IFNα2a could be a feasible treatment strategy for BS patients with TB or HBV infection.

There are some limitations of this study. Our cohort sample size was relatively small. However, given the rarity of BS patients with severe vascular/cardiac or neurological involvement who failed conventional therapy or other biologics, this study is already the largest cohort to date. Our study enrolled refractory BS patients who had received conventional treatment before standardized IFNα2a administration, which might have certain heterogenous in previous therapy. All patients recruited from a national referral center might induce potential selection bias. There has been no randomized controlled trial for IFNα2a in BS patients with vascular or neurological involvement. Further large prospective-controlled placebo-control studies to draw more definitive conclusions about the efficacy and safety of IFNα2a are warranted.

Conclusion

In conclusion, our study suggests that the concurrent use of IFNα2a, GCs, and immunosuppressants should be considered an effective therapeutic choice in refractory vascular/cardiac or neurological involvement in BS patients.

Declarations

Ethics approval and consent to participate

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

Consent for publication

All authors in this study agreed to publication.

Author contributions

Luxi Sun: Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing – original draft.
Yunxia Hou: Data curation; Formal analysis; Investigation; Writing – original draft.
Lifan Zhang: Data curation; Formal analysis; Software.
JinJing Liu: Data curation; Writing – review & editing.
Lu Li: Data curation; Investigation; Resources.
Zhimian Wang: Formal analysis; Methodology.
Xin Yu: Formal analysis; Methodology.
Menghao Zhang: Data curation; Investigation.
Xiaoqing Liu: Resources; Supervision.
Yan Zhao: Resources; Supervision.
Wenjie Zheng: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The clinical data used to support the findings of this study are included in the article.

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Supplemental material

Supplemental material for this article is available online.

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