THERAPEUTIC ADVANCES in
Chronic Disease

Original Research

Cyclosporin A as an adjunct may enhance the therapeutic effect of interferon alpha-2a in patients with refractory Behcet's uveitis: a retrospective cohort study

Ther Adv Chronic Dis

2024, Vol. 15: 1–12

DOI: 10.1177/20406223241304889

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Abstract

Background: The application of biologic agents has benefited patients with Behcet's uveitis (BU) who do not respond to conventional treatment regimens. However, there is currently no consensus on the optimal treatment regimen of interferon alpha-2a (IFN-α2a) for refractory BU.

Objectives: To evaluate treatment outcomes and safety of IFN-α2a in a large series of refractory BU patients and to explore whether nonbiologic immunomodulatory agents (cyclosporin A) other than corticosteroids should be concomitantly used.

Design: We conducted a retrospective cohort study, which included 153 BU patients who received IFN-α2a treatment between December 2012 and September 2023 with a minimum duration of 6 months.

Methods: Best-corrected visual acuity (BCVA), the frequency of uveitis relapse, corticosteroid-sparing effect, and side effects were evaluated.

Results: Of the 153 patients enrolled, 87 patients were treated with IFN-α2a plus corticosteroids (IC), and 66 patients were treated with IFN-α2a plus corticosteroids and cyclosporin A (ICC). Both IFN-α2a treatment regimens significantly improved BCVA as early as 2 months following treatment, and the improvement was maintained over at least a 2-year follow-up. At the final visit, 86.8% and 73.1% of the affected eyes in the ICC and IC groups achieved improved or stable vision, respectively. The ICC regimen was more effective at improving vision ($p = 0.01$). Overall, the frequency of uveitis relapse and the dose of oral prednisolone were significantly reduced in both groups after treatment (all $p < 0.0001$). However, there were no statistically significant differences in these parameters between the two groups. None of the included patients experienced serious side effects that led to the discontinuation of IFN-α2a therapy.

Conclusion: IFN-α2a treatment is a promising option for patients with refractory BU. Our results showed that cyclosporin A as an adjunct could enhance the therapeutic effect of IFN-α2a.

Keywords: Behcet's disease, cyclosporin A, interferon alpha-2a, uveitis

Received: 10 May 2024; revised manuscript accepted: 14 November 2024.

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Introduction

Behcet's disease (BD) is a complex, multi-system chronic inflammatory disorder characterized by occlusive vasculitis, mainly affecting young adults of reproductive age.[1] Ocular involvement frequently occurs in BD patients and is considered one of the most disabling and costly organ impairments.[2] Behcet's uveitis (BU) is the most

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common ocular manifestation in these patients, and dysfunctional T cell-mediated immunity is presumably involved in its development.[3,4] BU usually manifests as recurrent non-granulomatous panuveitis and retinal vasculitis, and is one of the most common uveitis entities leading to blindness.[1,5] Systemic corticosteroids combined with other nonbiologic immunomodulatory agents have been used for BU patients. However, some BU patients, with reports of up to 41.3%, show poor or no response to nonbiologic immunomodulatory agents even at optimal or maximum therapeutic doses.[6]

The recent introduction of biologic agents has benefited BU patients irresponsive to conventional treatment regimens.[7–9] Infliximab and adalimumab are the most common biologics used to treat BU. Another one is interferon alpha-2a (IFN-α2a). One recent retrospective study reported comparable outcomes between IFN-α2a and infliximab in patients with refractory BU.[10] However, no RCT-based evidence is available regarding the best treatment option in the case of nonbiologic immunomodulatory agents' failure. Physicians' preference for IFN-α2a or tumor necrosis factor-alpha (TNF-α) inhibitors relies on their experience and patient-related factors, such as financial burden, risk of latent infection reactivation, and potential side effects.[11,12] Given the lower cost of IFN-α2a than anti-TNF-α therapy in China, IFN-α2a may be a better choice for patients with refractory BU.[13] Since IFN-α2a was first applied to the treatment of refractory BU, many studies have reported its effectiveness and safety based on relatively small samples.[11,14,15] Therefore, studies on a large cohort of refractory BU patients on IFN-α2a treatment with a long-term follow-up are needed to provide more evidence of efficacy.

At present, there is no consensus on the optimal treatment regimen of IFN-α2a for refractory BU. Previous studies mostly used IFN-α2a in combination with corticosteroids. In recent years it has been increasingly recognized that this regimen is inadequate and unworkable for some more intractable BU patients.[13,16] Whether the concomitant use of IFN-α2a with nonbiologic immunomodulatory agents (such as cyclosporine A) other than corticosteroids would bring more benefits for refractory BU patients need to be explored.

This study aimed to evaluate treatment outcomes and safety of IFN-α2a for refractory BU in a large cohort with a relatively long-term follow-up. More importantly, we, for the first time, compared clinical outcomes of two regimens, namely IFN-α2a plus corticosteroids (IC) and IFN-α2a plus corticosteroids and cyclosporine A (ICC) on visual prognosis and uveitis recurrence.

Methods

This retrospective cohort study was conducted using the national uveitis database established by the Uveitis Center of the First Affiliated Hospital of Chongqing Medical University.[17,18] We consecutively extracted detailed medical records of 371 BU patients receiving IFN-α2a treatment between December 2012 and September 2023. All patients met the proposed international diagnostic criteria for BD.[19,20] Refractory BU patients treated with IFN-α2a regularly for at least 6 months were included in this study. Patients who did not take corticosteroids due to pre-existing steroid-induced femoral head necrosis and those who used cyclosporine A intermittently and irregularly were all excluded from this study. Therefore, a total of 153 refractory BU patients were included in this study. Refractory BU was defined as at least two or three relapses in the year before enrollment despite the use of corticosteroids and at least one nonbiologic immunomodulatory agent for a minimum of 1 year. Uveitis relapse was defined as a reappearance of intraocular inflammation such as anterior chamber cells, vitritis, or retinal vasculitis regardless of the severity, or worsening of pre-existing inflammation with reference to the Standardization of Uveitis Nomenclature (SUN) Working Group guidelines.[21] Retinal vasculitis was also determined according to the guidelines established by the SUN Working Group. All included patients were treated with IFN-α2a after signing a written informed consent. As described previously, IFN-α2a (3SBio Inc., Shenyang, China) subcutaneous injection was used with an initial dose of 3 million units daily for the first 3 months, decreased to every other day for another 3 months, and further tapered every 2 or 3 months.[22]

The enrolled patients could be further divided into two groups based on two regimens of IFN-α2a therapy. Before 2018, all patients received the IC regimen (known as the IC group). Briefly,

IFN-α2a was used only in combination with low-dose corticosteroids as previously reported, and thus all other nonbiologic immunomodulatory agents were discontinued before the initiation of IFN-α2a therapy.[22] Since 2018, all new refractory BU patients treated with IFN-α2a have been on the ICC regimen (known as the ICC group) due to the increasing reports of its beneficial effects in recent years. Cyclosporine A was the most commonly used nonbiologic immunomodulatory agent in our clinical practice due to the good performance we experienced clinically during past decades.[23] Therefore, the enrolled patients in the ICC group received cyclosporine A as a concomitantly used agent of IFN-α2a treatment. Cyclosporine A was used in parallel with IFN-α2a therapy until IFN-α2a administration was discontinued. The initial dose of cyclosporine A was 2–4 mg/kg/day, and this dosage was used for at least 6 months. In cases where the initial dosage was over 2 mg/kg/day, a reduction in the dose of cyclosporine A was made according to the improvement of intraocular inflammation or side effects. The therapeutic regimens before and after IFN-α2a initiation in both groups are shown in Table S1. For these two groups, the initial dose of systemic corticosteroids was 20 mg/day at the beginning of IFN-α2a treatment. The dose of corticosteroids was gradually reduced based on the improvement of intraocular inflammation.[24]

Data collected at the first visit and each follow-up visit for all patients, including demographics, medical history, treatment, ophthalmic examinations (slit-lamp microscopy, intraocular pressure, best-corrected visual acuity (BCVA), and ophthalmoscopy), auxiliary examinations if performed (optical coherence tomography, ultrasound biomicroscopy, fundus fluorescein angiography (FFA), B-scan ultrasonography, and color fundus photography), and necessary laboratory tests (routine blood test and serum biochemical test) were recorded into the database. The primary outcome measure was the rates of BCVA change (visual improvement, stabilization, and deterioration) during IFN-α2a therapy. The secondary outcome measures were changes in the number of uveitis relapses per patient-year, BCVA, and the dose of prednisone. Improved or deteriorated visual acuity was separately defined as a doubling or halving of the visual angle, corresponding to an increase or drop of three lines on a logarithmic visual acuity chart.[21]

SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and GraphPad software (GraphPad Prism version 8.3.0 for Windows, San Diego, CA, USA) were used to conduct statistical analyses. Quantitative data with normal distribution were presented as mean ± standard deviation (SD), and those with non-normal distribution were shown as median with interquartile range (IQR). Qualitative data were expressed as frequencies and percentages (*n*, %). Visual acuity for analysis was converted to a logarithm of the minimum angle of resolution (logMAR). For visual acuities of counting fingers or less, logMAR values were assigned as previously described.[25] Generalized estimating equation (GEE) was performed to adjust for the inter-eye correlation within the same subject. Baseline demographics and clinical characteristics were compared between the ICC and IC group using Student's *t* test, Mann–Whitney *U* test, Fisher exact test, Chi-square test (or with Yates' correction), or GEE as appropriate (Table 1, Tables S2 and S3). For the primary outcome analysis, characteristics with significance at baseline comparison ($p < 0.05$) were adjusted as potential confounders in GEE. Categorical baseline visual acuity, IFN-α2a treatment time, and follow-up time were finally used in the multivariable model (Table S4). Subgroup analysis was also performed according to baseline visual acuity. In addition, mean change in visual acuity from baseline at the specified time point was tested using GEE (Figure 1). Mann–Whitney *U* test, Wilcoxon matched-pairs signed-rank test, Fisher exact test, Chi-square test (or with Yates' correction), or log-rank test (for survival analysis) were performed for the secondary outcome analysis when appropriate. Differences were considered statistically significant when a two-sided *p* value was less than 0.05.

Results

Patient characteristics

Of the 153 patients enrolled, 66 were classified into the ICC group and 87 into the IC group. Overall, as shown in Table 1, the mean age at the uveitis onset and the initiation of IFN-α2a were 27.6 ± 8.3 and 32.2 ± 8.9 years, respectively. The overwhelming majority were male (88.9%). Bilateral involvement was observed in 138 patients (90.2%). All the patients had posterior segment involvement of the eye, including optic

Table 1. Characteristics of the patients at baseline.

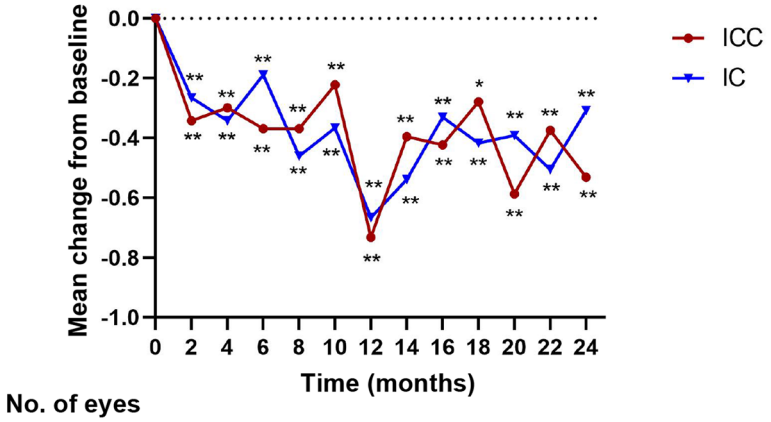
Characteristics	Total (*N* = 153, *n* = 270)	ICC (*N* = 66, *n* = 114)	IC (*N* = 87, *n* = 156)	*p* Value[a]
Age at onset (years)	27.6 ± 8.3	27.9 ± 9.1	27.4 ± 7.8	0.71
Male	136 (88.9%)	59 (89.4%)	77 (88.5%)	0.86
Age at IFN-α2a initiation (years)	32.2 ± 8.9	32.1 ± 9.4	32.3 ± 8.5	0.93
Duration of BU (months)	46.0 (28.0–75.5)	40.0 (24.0–71.0)	50.0 (30.0–81.0)	0.07
Duration of IFN-α2a treatment (months)	19.4 (12.4–32.7)	16.6 (12.4–25.2)	26.8 (12.1–39.1)	0.003
Total follow-up (months)	19.4 (12.4–34.1)	16.6 (12.4–26.1)	26.8 (12.1–41.5)	0.004
Bilateral involvement	138 (90.2%)	56 (84.8%)	82 (94.3%)	0.053
Relapse frequency (relapses/patient-year)	4.0 (2.0–6.5)	4.0 (2.0–7.2)	3.0 (2.0–6.0)	0.61
Baseline BCVA (LogMAR)	1.3 (0.7–2.1)	1.0 (0.4–2.1)	1.3 (0.8–2.1)	NA[b]
Categorical baseline BCVA				0.02
Baseline BCVA ⩽ 20/200	168 (62.2%)	61 (53.5%)	107 (68.6%)	
20/200 < Baseline BCVA ⩽ 20/50	63 (23.3%)	31 (27.2%)	32 (20.5%)	
Baseline BCVA > 20/50	39 (14.5%)	22 (19.3%)	17 (10.9%)	

Data are presented as mean ± SD, median (IQR), and no. (%).
[a]*p* values represent comparisons between the ICC and IC groups.
[b]NA, *p* value could not be obtained because the non-normal distribution of baseline logMAR BCVA prevented correction of the inter-eye correlation within the same subject.
BCVA, best-corrected visual acuity; BU, Behcet's uveitis; IC, patients treated with IFN-α2a plus corticosteroids; ICC, patients treated with IFN-α2a plus corticosteroids and cyclosporin A; IFN-α2a, interferon alpha-2a; IQR, interquartile range; LogMAR, logarithm of the minimum angle of resolution; NA, not applicable.

nerve head inflammation ($n = 69$, 25.6%), retinal infiltrates ($n = 87$, 32.2%), retinal vasculitis identified by FFA ($n = 264$, 97.8%), retinal vein occlusion ($n = 63$, 23.3%), and macular edema ($n = 96$, 35.6%). Of these patients, 131 individuals (85.6%) developed panuveitis. The median duration of BU before IFN-α2a treatment was 46 (IQR 28–75.5) months. The median IFN-α2a treatment period was 19.4 (IQR 12.4–32.7) months, with 67 patients being treated for more than 2 years. The median follow-up time was 19.4 (IQR 12.4–34.1) months. Of 153 patients, 119 patients were followed up for longer than 12 months. Table S2 summarizes the ocular complications of BU at baseline. Their previous extraocular manifestations are shown in Table S3. Generally, baseline characteristics were similar between the two groups except for the IFN-α2a treatment and follow-up time ($p = 0.003$ and $p = 0.004$, respectively) and distribution of baseline visual acuity ($p = 0.02$).

Outcomes of two regimens of IFN-α2a therapy

A total of 270 affected eyes from 153 BU patients were included in the IFN-α2a outcome analysis. Twenty-one eyes were excluded from this analysis due to severe optic and retinal atrophy resulting in no light perception before IFN-α2a treatment, without any possibility of improvement. Overall, the median logMAR BCVA of all affected eyes was significantly improved from 1.3 (IQR 0.7–2.1) at baseline to 0.9 (IQR 0.3–2.1) at the final visit after treatment ($p = 0.003$). As seen in Figure 1, two regimens of IFN-α2a therapy significantly improved visual acuity as early as 2 months after initiation of treatment, and the improvement was maintained at least for a 2-year follow-up. At the



No. of eyes

Time	0	2	4	6	8	10	12	14	16	18	20	22	24
ICC	114	66	59	64	41	34	29	14	32	20	19	14	31
IC	156	102	84	90	42	54	28	22	41	17	21	10	52

Figure 1. Changes in BCVA over time during IFN-α2a therapy.
The mean changes in logMAR BCVA from baseline at the specified time point after IFN-α2a treatment are shown. The generalized estimating equation was performed to test the significance of BCVA changes from baseline. Given the retrospective nature of this study, the patients included were not exactly followed up every 2 months. Therefore, the exact number of eyes with BCVA records at a specific time point is given at the bottom of the image.
*$p < 0.05$. **$p < 0.01$.
BCVA, best-corrected visual acuity; IC, patients treated with IFN-α2a plus corticosteroids; ICC, patients treated with IFN-α2a plus corticosteroids and cyclosporine A; IFN-α2a, interferon alpha-2a; LogMAR, the logarithm of the minimum angle of resolution.

final visit, 86.8% and 73.1% of the affected eyes in the ICC and IC groups achieved improved or stable vision, respectively. Moreover, we performed a subgroup analysis according to baseline visual acuity. The rate of visual stabilization or improvement in the eyes with a baseline BCVA equal to or below 20/200 was lower than that in the eyes with a baseline BCVA better than 20/50 (Table 2). Additionally, a notable improvement was observed in 58 (81.7%) out of 71 eyes with macular edema in patients who underwent optical coherence tomography evaluation before and after IFN-α2a treatment.

The frequency of uveitis relapse was significantly reduced from 4.0 (IQR 2.0–7.2) and 3 (IQR 2.0–6.0) relapses per patient-year before IFN-α2a treatment to 0.7 (IQR 0–1.8) and 0.8 (IQR 0–2.0) relapses per patient-year, respectively, in the ICC and IC groups (both $p < 0.0001$). The median time to the first relapse during treatment was 12 (IQR 7–16) and 9 (IQR 4.8–21.2) months in the ICC and IC groups, respectively. There was no uveitis recurrence in 57 patients (32.2% in the IC group and 43.9% in the ICC group) throughout the follow-up period.

The corticosteroid-sparing effect was achieved in both groups. As seen in Figure 2(a), oral prednisolone dose was obviously reduced at each time point compared to baseline during a 2-year follow-up period in both groups. At the last visit, the dose of oral prednisolone was reduced from baseline to 12.9 (IQR 7.5–16.9) mg/day in the ICC group and 12.5 (IQR 5–17.5) mg/day in the IC group (both $p < 0.0001$). Overall, in 40.5% of patients (42.5% in the IC group and 37.9% in the ICC group), the prednisolone dose was successfully reduced to 10 mg/day or less while maintaining inactive uveitis. We also noted that 29 patients (19.0%) successfully reduced their prednisolone dose to discontinuation throughout the follow-up period. In addition, 25 patients (16.3%) discontinued IFN-α2a treatment 6 months after the complete control of intraocular inflammation as well as systemic manifestations. The duration of

Table 2. Visual acuity outcomes of the patients treated with IFN-α2a.

Outcomes	Total ($n=270$)	ICC ($n=114$)	IC ($n=156$)	Adjusted OR (95% CI) (ICC vs IC)	Adjusted p value (ICC vs IC)
Change from baseline (overall)				2.5 (1.2–5.1)[a]	0.01
Visual stabilization or improvement	213 (78.9%)	99 (86.8%)	114 (73.1%)		
Visual deterioration	57 (21.1%)	15 (13.2%)	42 (26.9%)		
Subgroup analysis (stratified by baseline BCVA)					
Baseline BCVA ⩽ 20/200				2.5 (1.0–6.1)[b]	0.04
Visual stabilization or improvement	125 (74.4%)	52 (85.2%)	73 (68.2%)		
Visual deterioration	43 (25.6%)	9 (14.8%)	34 (31.8%)		
20/200 < Baseline BCVA ⩽ 20/50				2.5 (0.6–10.6)[b]	0.21
Visual stabilization or improvement	52 (82.5%)	27 (87.1%)	25 (78.1%)		
Visual deterioration	11 (17.5%)	4 (12.9%)	7(21.9%)		
Baseline BCVA > 20/50				0.5 (0.0–14.6)[b]	0.71
Visual stabilization or improvement	36 (92.3%)	20 (90.9%)	16 (94.1%)		
Visual deterioration	3 (7.7%)	2 (9.1%)	1 (5.9%)		

Data are presented as no. (%).
[a]Adjusted for the categorical baseline visual acuity and the IFN-α2a treatment and follow-up time.
[b]Adjusted for the IFN-α2a treatment and follow-up time.
BCVA, best-corrected visual acuity; CI, confidence interval; IC, patients treated with IFN-α2a plus corticosteroids; ICC, patients treated with IFN-α2a plus corticosteroids and cyclosporin A; IFN-α2a, interferon alpha-2a; OR, odds ratio.

their treatment was 40 ± 12.2 months, and they were followed up for 8 (IQR 5–13) months after discontinuation.

Comparisons of outcomes between the IC regimen and ICC regimen

To date, there is no consensus on the optimal regimen of IFN-α2a treatment for uveitis. In this study, we investigated whether cyclosporin A other than corticosteroids could act as an adjunct to enhance the effect of IFN-α2a in the management of refractory BU. As shown in Table 2, a higher proportion of improved or stable vision and a lower proportion of vision loss were observed in the ICC group as compared to the IC group ($p=0.01$). Furthermore, we performed a subgroup analysis in the context of the same level of baseline BCVA to exactly compare the visual prognosis. Notably, we found that in eyes with baseline BCVA equal to or below 20/200, the proportion of improved or stable vision in the ICC group was significantly higher than that in the IC group ($p=0.04$). However, in eyes with baseline BCVA better than 20/200, there was no difference concerning the visual outcome between these two groups.

We also compared the relapse frequency, the time to first relapse (Figure 2(b)), and the corticosteroid-sparing effect between these two groups after treatment. There were no statistically significant differences in all of these parameters.

Side effects

Of these 153 patients treated with IFN-α2a, flu-like symptoms were the most common side effect

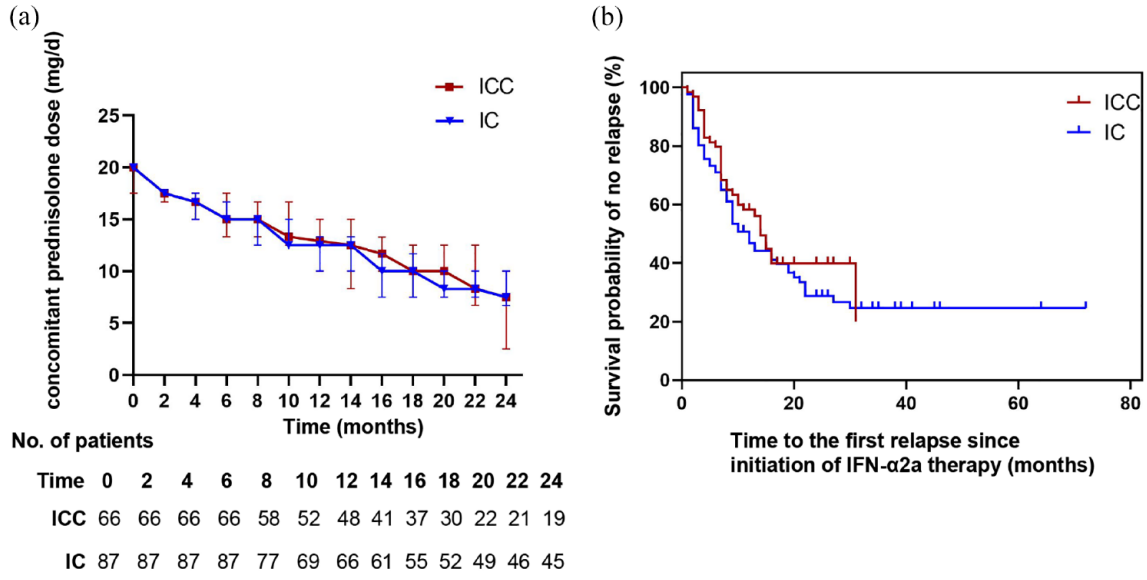


Figure 2. Changes in prednisolone dose over time and survival probability of no relapse during IFN-α2a therapy. (a) Changes in the prednisolone dose are shown during follow-up in the ICC and IC groups. Data are shown as the median and 95% confidence intervals. (b) Kaplan–Meier survival curves for the time to the first uveitis relapse are shown since the initiation of IFN-α2a therapy in the ICC and IC groups ($p = 0.3$).
IC, patients treated with IFN-α2a plus corticosteroids; ICC, patients treated with IFN-α2a plus corticosteroids and cyclosporine A; IFN-α2a, interferon alpha-2a.

(89.1%; $n = 131/147$), followed by fatigue (27.2%; $n = 40/147$), hair loss (19.7%; $n = 29/147$), arthralgia (17.0%; $n = 25/147$), gastrointestinal discomfort (16.3%; $n = 24/147$), mild/moderate elevation of serum liver enzymes (13.3%; $n = 15/113$), mild/moderate leukopenia or reduction in platelet counts (13.1%; $n = 14/107$), skin itch (7.5%; $n = 11/147$), insomnia (6.1%; $n = 9/147$), lethargy (4.8%; $n = 7/147$), mild depression (2.7%; $n = 4/147$), chest distress (0.6%; $n = 1/147$). There was no significant difference regarding the percentage of side effects between the ICC group and the IC group. These aforementioned side effects were considerably improved following the reduction of the IFN-α2a dose or the adjustment of the drugs concomitantly used.

Discussion

This study, to our knowledge, is the first one to compare the difference of therapeutic effect between patients treated with IC and those treated with ICC. Our results showed that the ICC regimen generally achieved a better visual prognosis as compared to the IC regimen, especially for patients with baseline BCVA equal to or below 20/200. Moreover, our findings, on the one hand, confirmed the efficiency of IFN-α2a in improving BCVA and reducing uveitis recurrence and corticosteroid doses. On the other hand, its early use is recommended for patients with contraindications for anti-TNF-α agents.

BU is a sight-threatening disease that can cause blindness if not treated appropriately and promptly, thus severely compromising patients' quality of life.[24] Given their targeted immunoregulatory properties, biologic therapies, especially infliximab and adalimumab, have been increasingly recognized to outperform conventional treatment options, providing better disease control and a more favorable safety profile for patients with sight-threatening uveitis involving the posterior segment.[26] Evidence from different countries also shows that IFN-α2a may provide additional benefits to refractory BU patients.[13,27–31] However, given the rarity of BU in certain countries, almost all previous studies had the limitation of a relatively small number of participants. Therefore, a large cohort study with enough long-term follow-up is necessary to further validate the effectiveness of IFN-α2a in previous studies. In this study, a large cohort consisting of 153 refractory BU patients treated with IFN-α2a were enrolled and

followed up for a relatively long time. Our results show that both IFN-α2a treatment regimens could significantly benefit BU patients when conventional treatment fails.

It is well known that the aim of treating BU is to preserve vision and prevent vision loss. Therefore, the evaluation of emerging drugs is mainly based on their success in maintaining vision.[32] Previous studies have suggested the beneficial effect of IFN-α2a in maintaining vision for BU patients, despite the diversity in its treatment regimens. Two recently published studies showed that BCVA was notably improved as early as 1 month after initiation of IFN-α2a.[11,14] Similarly, our results showed a significant improvement in BCVA at 2 months following treatment, and this improvement was maintained at least for a 2-year follow-up when compared to the baseline values. It is worth noting that visual acuity was observed to fluctuate over time, which may be attributed to factors such as irregular follow-up visits, variations in treatment adherence, and disease progression. Others' findings and ours further confirmed the advantage of IFN-α2a in inducing a rapid control of ocular inflammation and maintaining long-term remission.[12,27] One study from France reported stable or improved vision in 29 affected eyes (76.3%) after treatment with IFN-α2a.[33] In another study from Turkey, 84.3% of 16 patients obtained stable or improved visual acuity.[34] Impressively, up to 94.8% of the 53 patients from 1 German study achieved visual improvement or stabilization.[35] We also observed a beneficial effect, with 78.9% of the 270 affected eyes achieving visual stabilization or improvement (86.8% in the ICC group and 73.1% in the IC group). Interestingly, we found that eyes with baseline BCVA of more than 20/50 could achieve a better visual prognosis than those with baseline BCVA equal to or lower than 20/200. These findings, on one hand, could partially explain that the discrepancy in visual outcomes reported previously may arise from differences in BCVA at baseline and IFN-α2a regimens used in the treatment. On the other hand, our findings highlight the early use of IFN-α2a in the management of refractory BU patients.

Although IFN-α2a has been widely used to treat refractory BU, no consensus has been reached concerning its optimal treatment regimen. In previous studies, IFN-α2a was commonly administrated in combination with corticosteroids. Growing evidence shows that both IFN-α and corticosteroids can enhance the suppressive activity of Treg cells.[36,37] Their combination may synergistically strengthen immunosuppressive actions. The effect of concomitant use of IFN-α with other nonbiologic immunomodulatory agents remains controversial, as some scholars believe that other nonbiologic immunomodulatory agents might antagonize the effect of IFN-α.[38] However, in recent years, this concomitant use of IFN-α with other nonbiologic immunomodulatory agents has been increasingly shown to be effective and relatively safe for patients with more refractory or severe BU.[13,37] Our results also showed that the ICC group achieved an overall higher proportion of improved or stable vision compared to the IC group. Notably, we found that the significant difference in visual outcomes between the two groups depended on baseline visual acuity. In eyes with baseline BCVA equal to or below 20/200, the ICC regimen was more effective in improving vision. However, there were no differences between these two groups in the context of baseline BCVA better than 20/200. The development of anti-drug antibodies has been shown to be associated with a reduced response or non-response to IFN-α2a.[39] The concomitant use of nonbiologic immunomodulatory agents has been reported to reduce the immunogenicity of TNF inhibitors and decrease the formation of anti-drug antibodies.[40] It is likely that the concomitant use of IFN-α with cyclosporin A may also achieve this effect through the aforementioned mechanisms. More studies are needed to clarify the complex mechanisms of the combination of IFN-α2a with cyclosporin A.

Recurrent inflammatory episodes are a typical clinical feature of BU, and their frequency and severity eventually determine the visual prognosis.[41] As previously reported, this study also supports the opinion that IFN-α2a therapy can significantly reduce the frequency of uveitis relapse and thus improve visual outcomes.[13,22] Our study showed that 43.9% of patients in the ICC group and 32.2% in the IC group achieved complete control of uveitis throughout the follow-up period. In the remaining patients with recurrent uveitis, the median time to the first relapse during treatment was 12 months in the ICC group

and 9 months in the IC group. These findings indicated that both the ICC and IC regimes could effectively control intraocular inflammation, subsequently improving the patient's visual prognosis. However, there was no significant difference regarding the relapse frequency between the two regimes. Whether there is a difference in the severity of intraocular inflammation at each relapse between the two regimens needs to be further studied in the future. The effectiveness of IFN-α2a in tapering systemic corticosteroids while maintaining inactive uveitis was evaluated following the SUN's guidelines. Our study demonstrated that both IFN-α2a treatment regimens seem to achieve a successful corticosteroid-sparing effect, consistent with previous report.[33]

Several studies have reported that IFN-α2a treatment is also associated with the control of extraocular manifestations, such as genital ulcerations, arthritis, and skin lesions.[13,42] In this study, extraocular manifestations were not strictly analyzed mainly due to the lack of regular follow-up of these patients by relevant specialists such as rheumatologists and dermatologists. However, it is certain that none of the patients enrolled in this study developed new or severe extraocular manifestations during IFN-α2a treatment. According to the available incomplete data, we observed that 17 patients in the ICC group and 23 patients in the IC group reported notable improvement in their pre-existing extraocular manifestations during treatment. Meanwhile, two patients in the ICC group and six patients in the IC group reported no change in their symptoms.

As reported in previous studies, IFN-α2a-related side effects are common, but most are dose-dependent, reversible, and not severe enough to prevent its further use.[11,16] All patients enrolled in this study generally tolerated the IFN-α2a treatment well, although mild to moderate abnormalities, such as flu-like symptoms (fever, headache, and muscle pain), were observed in some patients. Mild or moderately elevated liver enzymes returned to normal levels in all these patients after adjustment of the dose of IFN-α2a and other drugs concomitantly used. Furthermore, we did not find an additionally increased percentage of the side effects in the ICC group, possibly due to the low dose of the drugs concomitantly used. Our study suggests that a low dose of cyclosporin A as an adjunct may have a synergistic effect with IFN-α2a but does not increase the risk of development of the side effect.

The retrospective design of this study was its major limitation. While it involved a large cohort, we did not conduct a sample size calculation prior to the study due to its retrospective nature. The beneficial effects of the ICC regimen observed in refractory Chinese BU patients are expected to be validated in other populations. Since no patients reported thyroid dysfunction, routine screening, and monitoring of thyroid function, as well as the assessment of serum autoantibodies, were not conducted in this study, which needs to be addressed in future research. As for the subgroup analysis, the lack of differences in visual outcomes between the two groups at better baseline BCVA levels needs to be further confirmed in a larger cohort. In this study, cyclosporine A was selected as a concomitantly used agent in the ICC regimen due to the good performance we experienced clinically during past decades. The effects of concomitant use of IFN-α2a with other nonbiologic immunomodulatory agents need to be further investigated in the future. Additionally, these patients had a long median duration of BU at enrollment due to their prior long-term treatment with nonbiologic immunomodulatory agents before their first visit to our uveitis center.

Conclusion

In conclusion, this study, with a relatively large cohort, offers further support for the therapeutic effect and safety of IFN-α2a in the management of patients with refractory BU. Our findings also suggest that initiating IFN-α2a treatment at an earlier stage may be more beneficial if BU is determined to be refractory inflammation. Importantly, our results showed that cyclosporine A may serve as an adjunct to IFN-α2a treatment for refractory BU patients, especially for those with a worse BCVA at the first visit. Future prospective multicenter studies are expected to further validate these findings.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board at the First Affiliated Hospital of Chongqing Medical University (2020-434). A

waiver of informed consent was granted by the institutional review board at the First Affiliated Hospital of Chongqing Medical University due to the retrospective study design and anonymized nature of the data. All study procedures were performed according to the tenets of the Declaration of Helsinki.

Consent for publication
Not applicable.

Author contributions
Peizeng Yang: Conceptualization; Data curation; Funding acquisition; Investigation; Project administration; Resources; Supervision; Writing – review & editing.

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Ziqian Huang: Data curation; Formal analysis; Investigation; Writing – review & editing.

Lingyu Dai: Data curation; Investigation; Writing – review & editing.

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Acknowledgements
None.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by National Natural Science Foundation Key Program (82230032, 81930023), Major Program of Medical Science and Technology Project of Health Commission of Henan Province (SBGJ202101011). The funding organization had no role in the design or conduct of this research.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Supplemental material
Supplemental material for this article is available online.

References
1. Deuter CM, Kötter I, Wallace GR, et al. Behçet's disease: ocular effects and treatment. *Prog Retin Eye Res* 2008; 27: 111–136.
2. Ozyazgan Y, Ucar D, Hatemi G, et al. Ocular involvement of Behçet's syndrome: a comprehensive review. *Clin Rev Allergy Immunol* 2015; 49: 298–306.
3. Deng Y, Zhang Y, Cai T, et al. Transcriptomic profiling of iris tissue highlights LCK signaling and T cell-mediated immunity in Behcet's uveitis. *J Autoimmun* 2022; 133: 102920.
4. Zhong Z, Su G, Kijlstra A, et al. Activation of the interleukin-23/interleukin-17 signalling pathway in autoinflammatory and autoimmune uveitis. *Prog Retin Eye Res* 2021; 80: 100866.
5. Yang P, Ohno S and Zierhut M. Editorial: new insights into uveitis: immunity, genes, and microbes. *Front Immunol* 2021; 12: 765377.
6. Celiker H, Kazokoglu H and Direskeneli H. Conventional immunosuppressive therapy in severe Behcet's uveitis: the switch rate to the biological agents. *BMC Ophthalmol* 2018; 18: 261.
7. Ksiaa I, Abroug N, Kechida M, et al. Eye and Behçet's disease. *J Fr Ophtalmol* 2019; 42: e133–e146.

8. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. *Ophthalmology* 2012; 119: 1575–1581.
9. Sobaci G, Erdem U, Durukan AH, et al. Safety and effectiveness of interferon alpha-2a in treatment of patients with Behçet's uveitis refractory to conventional treatments. *Ophthalmology* 2010; 117: 1430–1435.
10. Yalçindag N and Köse HC. Comparison of the treatment results for Behçet uveitis in patients treated with infliximab and interferon. *Ocul Immunol Inflamm* 2020; 28: 305–314.
11. Eser-Ozturk H and Sullu Y. The results of interferon-alpha treatment in Behçet uveitis. *Ocul Immunol Inflamm* 2020; 28: 498–504.
12. 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.
13. Shi J, Zhao C, Zhou J, et al. Effectiveness and safety of interferon α2a as an add-on treatment for refractory Behçet's uveitis. *Ther Adv Chronic Dis* 2019; 10: 2040622319847881.
14. Qian Y, Qu Y, Gao F, et al. Comparison of the safety and efficacy of interferon alpha-2a and cyclosporine-A when combined with glucocorticoid in the treatment of refractory Behçet's uveitis: a randomized controlled prospective study. *Front Pharmacol* 2021; 12: 699903.
15. Kötter I, Zierhut M, Eckstein AK, et al. Human recombinant interferon alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis. *Br J Ophthalmol* 2003; 87: 423–431.
16. Diwo E, Gueudry J, Saadoun D, et al. Long-term efficacy of interferon in severe uveitis associated with Behçet disease. *Ocul Immunol Inflamm* 2017; 25: 76–84.
17. Yang P, Zhong Z, Du L, et al. Prevalence and clinical features of systemic diseases in Chinese patients with uveitis. *Br J Ophthalmol* 2021; 105: 75–82.
18. Yang P, Du L and Ye Z. How to deal with uveitis patients? *Curr Mol Med* 2018; 17: 468–470.
19. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). 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.
20. Criteria for diagnosis of Behçet's disease. International study group for Behçet's disease. *Lancet* (*London, England*) 1990; 335: 1078–1080.
21. Jabs DA, Nussenblatt RB and Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005; 140: 509–516.
22. Yang P, Huang G, Du L, et al. Long-term efficacy and safety of interferon alpha-2a in the treatment of Chinese patients with Behçet's uveitis not responding to conventional therapy. *Ocul Immunol Inflamm* 2019; 27: 7–14.
23. Yang P. *Atlas of uveitis: diagnosis and treatment*. Singapore: Springer, 2021.
24. Yang P, Fang W, Meng Q, et al. Clinical features of Chinese patients with Behçet's disease. *Ophthalmology* 2008; 115: 312–318.e4.
25. Day AC, Donachie PH, Sparrow JM, et al. The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: report 1, visual outcomes and complications. *Eye* (*London, England*) 2015; 29: 552–560.
26. Li B, Li H, Huang Q, et al. Shaping the future of Behçet's uveitis management: a comprehensive review of efficacy, challenges, and prospects of biologic therapies. *Ophthalmol Ther* 2023; 12: 2295–2321.
27. Gueudry J, Wechsler B, Terrada C, et al. Long-term efficacy and safety of low-dose interferon alpha2a therapy in severe uveitis associated with Behçet disease. *Am J Ophthalmol* 2008; 146: 837–844.e1.
28. Onal S, Kazokoglu H, Koc A, et al. Long-term efficacy and safety of low-dose and dose-escalating interferon alfa-2a therapy in refractory Behçet uveitis. *Arch Ophthalmol* (*Chicago, IL: 1960*) 2011; 129: 288–294.
29. Lee JH, Lee CS and Lee SC. Interferon alpha-2a treatment for refractory Behcet uveitis in Korean patients. *BMC Ophthalmol* 2018; 18: 52.
30. Kavandi H, Khabbazi A, Kolahi S, et al. Long-term efficacy and safety of interferon α-2a therapy in severe refractory ophthalmic Behcet's disease. *Clin Rheumatol* 2016; 35: 2765–2769.
31. Krause L, Altenburg A, Pleyer U, et al. Longterm visual prognosis of patients with

ocular Adamantiades-Behçet's disease treated with interferon-alpha-2a. *J Rheumatol* 2008; 35: 896–903.

32. Al-Janabi A, El Nokrashy A, Sharief L, et al. Long-term outcomes of treatment with biological agents in eyes with refractory, active, noninfectious intermediate uveitis, posterior uveitis, or panuveitis. *Ophthalmology* 2020; 127: 410–416.
33. Bodaghi B, Gendron G, Wechsler B, et al. Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. *Br J Ophthalmol* 2007; 91: 335–339.
34. Hasanreisoglu M, Cubuk MO, Ozdek S, et al. Interferon alpha-2a therapy in patients with refractory Behçet uveitis. *Ocul Immunol Inflamm* 2017; 25: 71–75.
35. Deuter CM, Zierhut M, Möhle A, et al. Long-term remission after cessation of interferon-α treatment in patients with severe uveitis due to Behçet's disease. *Arthritis Rheum* 2010; 62: 2796–2805.
36. Seissler N, Schmitt E, Hug F, et al. Methylprednisolone treatment increases the proportion of the highly suppressive HLA-DR(+)-Treg-cells in transplanted patients. *Transplant Immunol* 2012; 27: 157–161.
37. Lightman S, Taylor SRJ, Bunce C, et al. Pegylated interferon-α-2b reduces corticosteroid requirement in patients with Behçet's disease with upregulation of circulating regulatory T cells and reduction of Th17. *Ann Rheum Dis* 2015; 74: 1138–1144.
38. Kötter I, Günaydin I, Treusch M, et al. The use of interferon-alpha in Behçet's disease—review of the literature and possible mechanisms of action. *Adv Exp Med Biol* 2003; 528: 503–509.
39. Tamilvanan S, Raja NL, Sa B, et al. Clinical concerns of immunogenicity produced at cellular levels by biopharmaceuticals following their parenteral administration into human body. *J Drug Target* 2010; 18: 489–498.
40. Thomas SS, Borazan N, Barroso N, et al. Comparative immunogenicity of TNF inhibitors: impact on clinical efficacy and tolerability in the management of autoimmune diseases. A systematic review and meta-analysis. *BioDrugs clinical immunotherapeutics, biopharmaceuticals and gene therapy* 2015; 29: 241–258.
41. Tugal-Tutkun I and Çakar Özdal P. Behçet's disease uveitis: is there a need for new emerging drugs? *Expert Opin Emerg Drugs* 2020; 25: 531–547.
42. Kötter I, Vonthein R, Zierhut M, et al. Differential efficacy of human recombinant interferon-alpha2a on ocular and extraocular manifestations of Behçet disease: results of an open 4-center trial. *Semin Arthritis Rheum* 2004; 33: 311–319.