Correspondence on 'A pilot study of tofacitinib for refractory Behçet's syndrome'

We carefully read the recent study by Liu *et al* on the effectiveness of tofacitinib for refractory Behçet's syndrome (BS).[1] In total, 13 patients with BS were enrolled, including 5 cases with vascular involvement, 7 with gastrointestinal (GI) ulcers and one suffering polyarthritis. As an add-on approach, tofacitinib improved the outcomes in all patients with vascular lesions, but unchanged or worsened in 5/7 GI involvement cases. Their observation give support to the hypothesis that BS is not an independent disease, but a heterogeneous and multisystemic complex syndrome.[2] Different major organ involvements, vascular and GI involvement could link to its unique underlying immunopathological mechanisms, which led to radical treatment responses.[3] In their study, the only manifestation of ocular involvement was scleritis in one patient with polyarthritis, which is not a specific ophthalmological feature of BS. Notably, uveitis is one of the specific features of ocular involvement in patients with BS,[4] which may lead to visual loss in up to 25% of patients in spite of biological agents.[5] Here, we reported the efficacy and safety profile of tofacitinib in patients with refractory BU in our BS cohort from Huadong Hospital, Fudan University.

Thirteen patients were enrolled according to International Criteria for BS.[6] After enrolment, 5 mg tofacitinib was administered two times a day; prednisone was decreased to 30 mg/day and gradually tapered down; immunosuppressants were withdrawn. The efficacy assessment was conducted at each visit, including clinical manifestations, comprehensive eye examinations including visual acuity (VA), slit lamp and funduscopy. Optical coherence tomography and fundus fluorescein angiography were used. The disease activity was measured by Behçet's Disease Current Activity Form (BDCAF).[7] Success was defined by a two-step decrease in the level of inflammation and/or the disappearance of inflammatory signs.[8] Uveitis flare was defined by a two-step increase in the level of inflammation.

The baseline demographic data are shown in figure 1. The follow-up ranged from 24 to 38 months; BDCAF decreased from 5 (IQR 4–5) to 0 (IQR 0–1.5), p=0.001. Treatment success was achieved in 10 (76.9%) cases, experiencing a rapid and sustained improvement in VA, intraocular inflammation. Before tofacitinib initiation, the median VA (tumbling E chart) 0.25 (LogMAR equivalent 0.602) (IQR 0.2–0.3) improved to 0.8 (LogMAR equivalent 0.097) (IQR 0.6–0.8), p<0.001 at the last follow-up. There was a significant resolve of inflammation in anterior chamber cells from a median of 1 (IQR 0–2) to 0 (IQR 0–0), p<0.01 and vitritis from a median of 1 (IQR 2–3) to 0 (IQR 0–1), p<0.01.

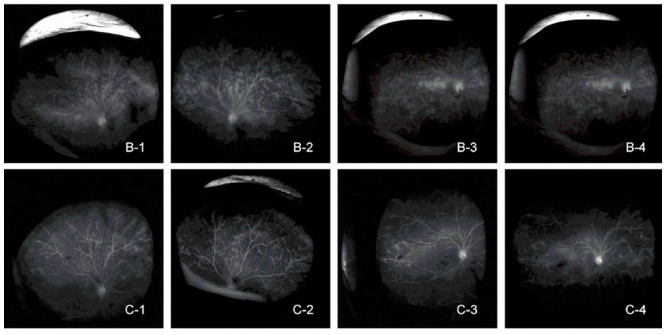
The median uveitis flare decreased substantially from 2 (IQR1-4) per patient year before Tofacitinib treatment to 0 (range 0–2) per patient year at the last visit, p=0.011. At the end of follow-up, uveitis was successfully controlled without relapse by tofacitinib 5 mg two times a day in four patients; tofacitinib was successfully tapered down to 5 mg daily in six cases. Corticosteroid was withdrawn in 10 patients and remained at 15 mg in 3 flare subjects. The treatment was well tolerated; only one case of herpes zoster was recorded. No thromboembolism and other events were documented.

Tofacitinib, a JAK1/3 inhibitor targeting the innate and adaptive immune compartments, has been proven effective in other inflammatory disorders, except for BS.[9 10] JAK-STAT signalling pathway and their corresponding cytokines have been implicated in the pathogenesis of BS.[11] Tofacitinib inhibits JAKs which in turn blocks the signalling of interleukin (IL)-2, IL-4, IL-6, IL-23, interferon (IFN)-γ and IFN-α.[12] Rapid resolve inflammation is critical in the treatment of BS. As a small molecule, tofacitinib may more efficiently cross the blood-retinal barrier, as compared with conventional and biological disease-modifying antirheumatic drugs. It should be noted that tofacitinib is a superb option for patients with uveitis.

In conclusion, our findings broaden the knowledge of the potential role of tofacitinib in refractory BU by markedly improving the VA and reducing uveitis flare.

No.	Sex	Age (yrs)	uveitis course (mths)	uveitis sites	Extraocular findings	Previous regiments combined with high dose GC	Regiments before TOF initiation	Regiments added TOF 5 mg, twice daily after enrolment	Follow-up (mths)	Clinical response
1	M	24	10	Bilateral	RAU, GU	CTX, CsA, AZA, IFX, ADA, TAC, CPT	Pred 100 mg/day +THD+COL+TAC	Pred 30 mg/day +THD	38	Success
2	M	37	4	OS	RAU, SL	CsA, IFX, THD, COL	Pred 50 mg/day +THD+COL+CsA	Pred 30 mg/day	32	Success
3	F	48	4	OS	RAU, SL	CsA, CTX, THD, COL	Pred 50 mg/day +COL+CsA	Pred 30 mg/day +COL	31	Success
4	M	44	10	OD	RAU, SL	CsA, THD, COL	Pred 50 mg/day +THD+COL+CsA	Pred 30 mg/day +THD	24	Success
5	M	40	8	OS	RAU, SL	CsA, IFX, COL	Pred 60 mg/day +THD+COL+CsA	Pred 30 mg/day +THD	25	Success
6	M	37	8	OS	RAU, GU	CsA, IFX, COL	Pred 60 mg/day +COL+CsA	Pred 30 mg/day +COL	34	Success
7	M	30	6	Bilateral	RAU, SL	CsA, THD, COL	Pred 100 mg/day +THD+COL+CsA	Pred 30 mg/day +COL	25	Success
8	M	31	10	Bilateral	RAU, SL	CsA, THD, COL	Pred 50 mg/day +THD+COL+CsA	Pred 30 mg/day +COL	24	Flare
9	M	30	7	Bilateral	RAU, GU, SL	CsA, THD, COL	Pred 50 mg/day +THD+COL+CsA	Pred 30 mg/day +COL	24	Success
10	F	17	4	Bilateral	RAU, GU, SL, A	CsA, THD, COL	Pred 50 mg/day +THD+COL+CsA	Pred 30 mg/day	24	Success
11	M	25	10	Bilateral	RAU, GU, SL, A	CsA, THD, COL	Pred 50 mg/day +THD+COL+CsA	Pred 30 mg/day	26	Success
12	M	25	6	Bilateral	RAU, GU, SL, V	CsA, IFX, THD, COL	Pred 60 mg /day +THD+COL+CsA	Pred 30 mg/day +COL	25	Flare
13	M	59	12	OS	RAU, GU, SL, A, CNS	CsA, IFX, HCQ, COL	Pred 50 mg /day +THD+COL+CsA	Pred 30 mg/day	26	Flare

A



B

Figure 1 Baseline characteristics in patients with refractory adamantiades-Behçet's uveitis and fundus fluorescein angiography of case number 9 at baseline and follow-up. (A) The demographic and clinical characteristics of the patients. A, arthralgia/arthritis; ADA, adalimumab; CNS central nervous system; COL, colchicine; CST, corticosteroid pulse therapy; CSA, cyclosporine; CTX, cyclophosphamide; GC, glucocorticoid; GU, genital ulcerations; HCQ, hydroxychloroquine; IFX, infliximab; Mths, months; OD, oculus dextrus; OS, oculus sinister; RAU, recurrent aphthous ulcer; Pred, prednisone; SL, skin lesions; TOF, tofacitinib; TAC, tacrolimus; THD, thalidomide; V, vasculitis; Yrs, years. (B) A 30-year-old male patient (case number 9) with retinal vascular leakage was confirmed by fundus fluorescein angiography in his right eye at baseline. (C) After 4 months treatment of tofacitinib 10 mg daily, retinal vascular leakage in his right eye resolved.

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Contributors JZ and C-HL participated in follow-up, provided the figure and wrote the manuscript. JZ performed statistical analysis. C-HL and YW collected the clinical

data at baseline. JZ, C-HL and YS helped to prepared the table. JZ, YS and J-LG provided critical revisions to the manuscript. J-LG designed the study, contributed to the discussion and edited the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by the National Natural Science Foundation of China (81871276).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Institutional review board of Huadong Hospital, Shanghai, China.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Zou J, Lin C-H, Wang Y, *et al*. *Ann Rheum Dis* 2023;**82**:e100.

Received 28 December 2020
Accepted 30 December 2020
Published Online First 25 January 2021

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-219828

Ann Rheum Dis 2023;**82**:e100. doi:10.1136/annrheumdis-2020-219810

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