Tofacitinib in refractory adult-onset Still's disease: 14 cases from a single centre in China

Adult-onset Still's disease (AOSD) is an autoinflammatory disease characterised by spiking fever, rash, polyarthralgia, sore throat and even life-threatening complications, such as macrophage activation syndrome and fulminant hepatitis. Excessive and inappropriate production of cytokines is a cornerstone in AOSD pathogenesis.[1] Unlike anakinra and tocilizumab, Janus kinases (JAK) inhibitors block the proinflammatory effect of a wide range of cytokines. This range of activity could be beneficial in AOSD patients who are refractory to or intolerant of treatment with biologicals. Anti-interleukin 1 (IL-1) agents are not available in mainland China. Tofacitinib, a JAK1/3 inhibitor, has been proven efficacious in several inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus and psoriasis arthritis.[2] To our interest, a case report observed that tofacitinib could ameliorate arthritis in a 13-year-old girl with recalcitrant systemic juvenile idiopathic arthritis,[3] which is the juvenile counterpart of AOSD.[4] Moreover, a JAK1/2 inhibitor, baricitinib has been reported effective in a 43-year-old patient with refractory AOSD.[5] Therefore, JAK inhibitors may be a novel therapeutic approach for refractory AOSD.

In our study, we aim to describe, to our knowledge for the first time, the efficacy of tofacitinib in 14 patients with refractory AOSD. All patients fulfilled Yamaguchi's criteria and were classified as refractory AOSD as defined previously.[6] They were followed up for the shortest of 1 month and the longest for 24 months by the same medical team. The evaluation of tofacitinib treatment was conducted at each visit, including clinical manifestations, laboratory tests, including white cell count (WBC) count, neutrophil per cent, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and ferritin, as well as glucocorticoids dosage adjustment. The AOSD disease activity was measured by a modified Pouchot's systemic score,[7] and adverse events were also recorded. The effectiveness of treatment was defined previously[8]: effective treatment was considered when all

Table 1 Baseline information of the AOSD patients at enrolment

No.	G	Age	Disease duration (months)	Clinical manifestations	Previous treatments	Treatments before JAKi initiation	Treatments after enrolment	Follow-up (months)	Clinical evaluation	CR time with JAKi (months)	Present pred dose (mg/day)
1	F	33	12	Polyarthritis, rash	CTX, MTX, CsA, NSAIDs iguratimod, thalidomide,	Pred 40 mg+tocilizumab	Pred 40 mg+JAKi 5 mg two times per day	24	Effective	16	2.5
2	F	27	6	Fever, polyarthritis	/	Pred 60 mg+MTX+CsA	Pred 60 mg+MTX+ JAKi 5 mg two times per day	13	Effective	5	5
3	F	32	48	Fever, rash, sore throat, myalgia	Thalidomide	Pred 30 mg+CsA+HCQ	Pred 50 mg+HCQ+ JAKi 5 mg two times per day	12	Effective	7	5
4	F	58	24	Polyarthritis, rash	Tocilizumab	Pred 10 mg+MTX+HCQ+CsA	Pred 15 mg+MTX+HCQ +JAKi 5 mg two times per day	6	Relapse when the pred dose was reduced to 2.5 mg/day	1	/
5	F	35	24	Polyarthritis, rash	Tocilizumab, thalidomide	Pred 10 mg+MTX+HCQ+LEF	Pred 15 mg+MTX +JAKi 5 mg two times per day	1	Partially effective	/	/
6	F	29	10	Polyarthritis, early joint destruction, lymphnodemegaly, MAS	/	Pred 100 mg+MTX	Pred 60 mg+MTX +JAKi 5 mg two times per day	9	Effective	6	7.5
7	F	72	5	ESR↑	/	Pred 30 mg+HCQ	Pred 25 mg+HCQ+ JAKi 5 mg one time per day	9	Effective	3	5
8	F	25	19	Polyarthritis	CsA, HCQ	Pred 50 mg+MTX	Pred 50 mg+MTX +JAKi 5 mg two times per day	4	Partially effective	/	15
9	F	41	60	Polyarthritis	/	Pred 120 mg+MTX+NSAIDs	Pred 60 mg+MTX+ JAKi 5 mg two times per day	5	Partially effective	/	/
10	F	31	12	Polyarthritis	/	Pred 20 mg+MTX+HCQ+CsA	Pred 20 mg+MTX + HCQ+CsA +JAKi 5 mg one time per day	4	Effective	4	5
11	F	33	1	Fever, rash, sore throat, polyarthritis, myalgia	/	Pred 60 mg+MTX+HCQ	Pred 40 mg+MTX +HCQ +JAKi 5 mg two times per day	3	Effective	2	20
12	M	35	4	MAS	VP16, DX	Pred 25mg+CsA+anakinra	Pred 22.5 mg +CsA+anakinra +JAKi 5 mg two times per day	1	Partially effective	/	17.5
13	M	18	22	Polyarthritis, rash	/	Pred 20 mg+MTX	Pred 15 mg+HCQ+ JAKi 5 mg two times per day	1	Partially effective	/	10
14	F	18	10	MAS, polyarthritis, rash	NSAIDs, IVIG	Pred 50 mg+CsA+tocilizumab	Pred 50 mg+CsA+MTX +JAKi 5 mg two times per day	1	Partially effective	/	35

CR, complete remission; CsA, cyclosporine; CTX, cyclophosphamide; DX, dexamethasone; ESR, erythrocyte sedimentation rate; F, female; G, gender; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin; JAK, Janus kinases; JAKi, JAK inhibitor, tofacitinib; LEF, leflunomide; M, male; MAS, macrophage activation syndrome; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; Pred, prednisone; VP16, etoposide.

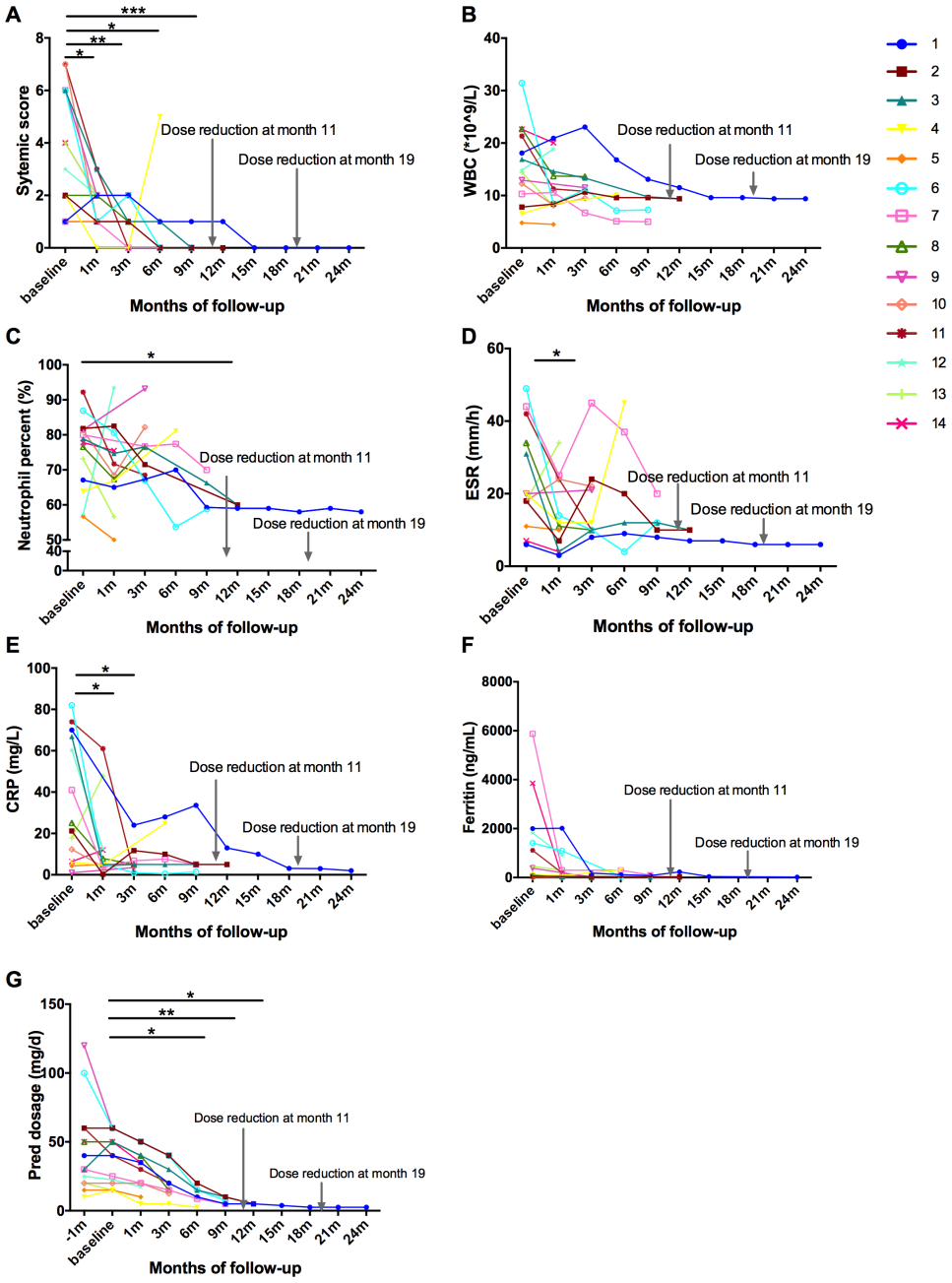

Figure 1 Contribution of improving systemic inflammation and sparing glucocorticoid dose with tofacitinib therapy. (A) Changes in systemic score in adult-onset Still's disease patients from baseline. (B–F) White cell count (WBC) count, neutrophil per cent, erythrocyte sedimentation rate (ESR), CRP levels and ferritin levels from baseline. (G) Glucocorticoid-sparing effects of tofacitinib administration. All data were statistically analysed using SPSS V.23.0. *p<0.05, **p<0.01, ***p<0.001.

initial clinical manifestations and abnormal laboratory tests had resolved, meaning achieving complete remission; partially effective treatment was considered when all but one initial clinical manifestation or abnormal laboratory test had resolved, meaning achieving partial remission; ineffective treatment was considered when two or more clinical manifestations or abnormal laboratory tests persisted.

The demographic data and clinical characteristics of the 14 patients are detailed in table 1. Seven of 14 (50%) AOSD patients achieved complete remission with decreased prednisone, six patients achieved partial remission and one relapsed when reduced the dosage of prednisone to 2.5 mg/day (table 1). Totally, four patients terminated tofacitinib: two patients were for partial remission, one for menometrorrhagia and one for relapse. Two patients reduced the dosage of tofacitinib to 5 mg/day and no relapses were observed after the adjustment. After application of tofacitinib for 1 month, seven patients quickly achieved complete resolution of fever and rashes, eight of polyarthritis. The systemic score was quickly reduced after 1 month, and completely improved at month 9 (figure 1A). WBC, neutrophil per cent, ESR, CRP and ferritin were decreased (figure 1B–F). The average dose of prednisone was significantly decreased from 37.3 mg/day to 5.0 mg/day at month 12 (figure 1G). Adverse events occurred in two patients. One had diarrhoea and increased heart rate and the other had menometrorrhagia. The first one continued the therapy, and the second stopped tofacitinib when achieved complete remission.

The cytokine storm activated by neutrophils and macrophages is strongly implicated in AOSD pathogenesis.[1] Tofacitibib inhibits the effect of IL-6, IL-10, IFN-γ, INF-α and granulocyte macrophage-colony stimulating factor (GM-CSF), thus suppressing neutrophils NOD-like receptor family pyrin domain-containing 3 (NLRP3) activation and IL-1β production.[9] Tofacitinib also suppresses macrophage activation and function.[10] It provides some experimental evidence to use tofacitinib in refractory AOSD.

In conclusion, application of tofacitinib in refractory AOSD patients contributes to disease remission/revolution and sparing corticosteroid dosage, especially these with polyarthritis.

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