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, polyarthritis, 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. 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. To our interest, a case report observed that tofacitinib could ameliorate arthritis in a 13-year-old girl with recalcitrant systemic juvenile idiopathic arthritis, which is the juvenile counterpart of AOSD. Moreover, a JAK2 inhibitor, baricitinib has been reported effective in a 43-year-old patient with refractory AOSD. 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. 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, and adverse events were also recorded. The effectiveness of treatment was defined previously: effective treatment was considered when all

| No. | G | Age | Disease duration (months) | Clinical manifestations | Previous treatments | Treatments before JAKi initiation | Treatments after enrolment | Follow-up (months) | CR time with JAKi (months) | Present pred. dose (mg/day) |
|-----|---|-----|--------------------------|------------------------|---------------------|-------------------------------|---------------------------|---------------------|----------------------------|--------------------------|
| 1   | F | 33  | 12                       | Polyarthritis, rash    | CTX, MTX, CsA, NSAIDs, thalidomide, 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          | 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+CsA       | 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                        | ESRI                  | /                    | 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 25 mg+CsA+anakinera     | Pred 22.5 mg+CsA+anakinera+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+thalidomide  | 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.
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. Tofacitinib 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 (NLPR3) activation and IL-1β production. Tofacitinib also suppresses macrophage activation and function. 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.

Qiongyi Hu, Mengyan Wang, Jinchao Jia, Jialin Teng, Huihui Chi, Tingting Liu, Hong-pei Liu, Xiaobing Cheng, Junna Ye, Yutong Su, Yue Sun, Zhuochao Zhou, Liyan Wan, Zhihong Wang, Fan Wang, Hui Shi, Chengde Yang

Department of Rheumatology and Immunology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence to Chengde Yang, Department of Rheumatology and Immunology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; yangchengde@sina.com Dr Hui Shi; shihui_jtj@sina.com

Handling editor Josef S Smolen

Contributors QH participated in follow-up, provided the figure and wrote the manuscript. MW performed statistical analysis. JJ and JT collected the clinical data at baseline. HC, TL and HL helped to prepare the table. XC, JY and Yutong Su accessed the disease activity of AOSD patients. Yue Sun, ZZ and LW analysed the data and baseline. HC, TL and HL helped to prepare the table. XC, JY and Yutong Su accessed the disease activity of AOSD patients. Yue Sun, ZZ and LW analysed the data and baseline. WX and FW helped to following up. HG performed statistical analysis. JW and MW contributed equally.

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Information on demographic and clinical data were obtained under a protocol approved by the Institutional Research Ethics Committee of Ruijin Hospital (ID: 2016-62), Shanghai, China. All participants signed written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

OPEN ACCESS

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

QH and MW contributed equally.

To cite Hu Q, Wang M, Jia J, et al. Ann Rheum Dis 2020;79:842–844.

Received 24 November 2019

Revised 4 February 2020

Accepted 5 February 2020

Published Online First 20 February 2020

REFERENCES

1 Hu Q, Shi H, Zeng T, et al. Increased neutrophil extracellular traps activate NLPR3 and inflammatory macrophages in adult-onset Still’s disease. Arthritis Res Ther 2019;21:9.

2 Jamiloulou Y, El Jammal T, Vuittom L, et al. Jak inhibitors for the treatment of autoimmune and inflammatory diseases. Autoimmune Rev 2019;18:10290.

3 Huang Z, Lee P-Y, Yao X, et al. Tofacitinib treatment of refractory systemic juvenile idiopathic arthritis. Pediatrics 2019;143. doi:10.1542/peds.2018-2845. [Epub ahead of print: 04 Apr 2019].

4 Wang R, Li T, Ye S, et al. Application of MS score in macrophage activation syndrome patients associated with adult onset Still’s disease. Ann Rheum Dis 2019;annrheumdis-2019-216286.

5 Ladhari C, Jorgensen C, Pers YM. Treatment of refractory adult onset Still’s disease with combination anakinra and baricitinib therapy. Rheumatology 2019;58:736–7.

6 Li T, Gu L, Wang X, et al. A pilot study on tocilizumab for treating refractory adult-onset Still’s disease. Sci Rep 2017;7:13477.

7 Rau M, Schiller M, Krienke S, et al. Clinical manifestations but not cytokine profiles differentiate adult-onset Still’s disease and sepsis. J Rheumatol 2010;37:2369–76.

8 Verroustie F, Barretche T, Lazar E, et al. Adult-Onset Still’s disease biological treatment strategy may depend on the phenotypic dichotomy. Arthritis Res Ther 2019;21:53.

9 Funuya MY, Asaro T, Sumichika Y, et al. Tofacitinib inhibits granulocyte-macrophage colony-stimulating factor-induced NLPR3 inflammasome activation in human neutrophils. Arthritis Res Ther 2018;20:196.

10 De Vries LCS, Duarte JM, De Kriger M, et al. A JAK1 selective kinase inhibitor and tofacitinib affect macrophage activation and function. Inflamm Bowel Dis 2019;25:647–60.