Sequential tocilizumab and tofacitinib treatment for systemic juvenile idiopathic arthritis: a case report

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Case Report

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Abstract

Background: Systemic juvenile idiopathic arthritis (sJIA) is complex, difficult to cure, and has high morbidity and mortality rates. Herein, we report a case of a patient with sJIA who was treated with sequential tocilizumab and tofacitinib treatment.

Case presentation: The patient was a 4-year-old girl who was hospitalised with recurrent fever and polyarticular pain in June 2020. Laboratory tests revealed a white blood cell count of 15.32×10^9/L, platelet count of 676.8×10^9/L, serum ferritin level of 1,103.8 U/L, erythrocyte sedimentation rate of 85.00 mm/h, c-reactive protein level of 146.00 g/L, and interleukin (IL)-6 level of 287.95 pg/ml. Rheumatoid factor and antinuclear antibody results were negative, and she was diagnosed with sJIA. The patient was started on a combination of ibuprofen, methotrexate, and tocilizumab, and her temperature decreased to the normal range without any recurrence. The painful joint swellings resolved significantly after 3 months of follow-up. Janus kinase (JAK) inhibitors inhibit the effects of many cytokines, particularly IL-6, and is economical and convenient. Therefore, we selected tofacitinib to replace tocilizumab for her treatment, whereas the other drugs remained unchanged. Arthritis symptoms disappeared gradually after 9 months of follow-up. In May 2021, due to a slight recurrence of upper respiratory tract infection, the patient was hospitalised, administered one dose of tocilizumab, and continued to take oral tofacitinib, which quickly relieved the patient's symptoms. By December 2021, the patient's condition was stable.

Conclusions: The efficacy of treatment with sequential tofacitinib via tocilizumab in our patient with sJIA was found to be remarkable. IL-6 inhibitors sequential to JAK inhibitors could be a new option for the treatment of systemic juvenile idiopathic joints.

Background

Systemic juvenile idiopathic arthritis (sJIA) is the most severe subtype of juvenile idiopathic arthritis (JIA). sJIA differs from other forms of JIA, in that it is associated with significant systemic inflammatory features, such as fever and rash, in addition to arthritic manifestations; moreover, intrinsic immune abnormalities and autoantibodies are usually absent. The treatment options for sJIA are based on nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and disease-modifying anti-rheumatic drugs (DMARDs) and biological DMARDs (bDMARDs). However, difficulties in managing and controlling sJIA are still noted in some patients with systemic symptoms and arthritic manifestations or in those who present with serious drug side effects or complications. In recent years, the treat to target (T2T) model in paediatric rheumatic diseases has been gradually developed, wherein controlling symptoms and signs; preventing structural damage; avoiding co-morbidity and drug toxicity; optimising function, growth, and development; and improving disease-related quality of life and social participation have become treatment targets [1]. In achieving T2T, the use of bDMARDs, such as interleukin (IL)-1 or IL-6 inhibitors, is extremely important, resulting in a significantly improved prognosis for sJIA patients. However, IL-1 inhibitors have not been approved for the treatment of sJIA in mainland China, and only the

IL-6 receptor antagonist tocilizumab (TCZ) has been approved for the treatment of sJIA. Moreover, patients require alternative treatment options due to factors such as challenging treatment regimens involving long-term intravenous infusion and family financial constraints. Tofacitinib, a first-generation Janus kinase (JAK) inhibitor, primarily blocks the JAK1/JAK3 pathway, thereby inhibiting the release of multiple cytokines, including IL-6 [2].

Herein, we report the case of a patient with sJIA treated successfully with sequential TCZ and tofacitinib treatment, with an aim to provide a practical basis for the future use of tofacitinib as an alternative treatment option to IL-6 receptor antagonists.

Case Presentation

A 4-year-old girl (height 110 cm, weight 20 kg) presented with chief complaints of fever and polyarticular swelling and pain. In October 2019, the patient developed chills and fever with temperature of up to 39.5°C, which was treated with intermittent oral dexamethasone tablets. The fever resolved but recurred after discontinuation of the drug. Unfortunately, over the next 3 months, the patient attempted to discontinue dexamethasone, but her condition deteriorated rapidly, with persistent high fever and concurrent symmetric polyarticular swelling and pain involving almost all the joints of the body. Polyarticular swelling and pain were mainly reported in the bilateral proximal interphalangeal joints, bilateral metacarpophalangeal joints, bilateral wrists, bilateral elbows, bilateral knees, bilateral ankles, and bilateral metatarsal toes, with morning stiffness lasting more than 4 hours. The patient's daily life was severely affected, wherein she was unable to walk and required others' support. In February 2020, she visited several hospitals and received various treatments, such as ibuprofen suspension (3 ml/3 times/day, orally), dexamethasone injection (3 mg, intramuscularly, once), traditional Chinese medicine, and etanercept (12.5 mg, subcutaneously, twice), but her fever and arthritis symptoms showed little improvement.

Due to recurrent fever and persistent polyarticular swelling and pain, the patient was admitted to our department in June 2020. Physical examination showed swelling and tenderness in the proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints, and she was uncooperative with the Patrick's test. Laboratory tests revealed a white blood cell count of 15.32 × 10^9/L, haemoglobin level of 91.8 g/L, platelet count of 676.8 × 10^9/L, serum ferritin level of 1,103.8 U/L, erythrocyte sedimentation rate (ESR) of 85.00 mm/h, c-reactive protein (CRP) level of 146.00 g/L, significantly elevated cytokine IL-6 level at 287.95 pg/ml, alanine transaminase level of 53.3 U/L, and albumin level of 26 g/L. Blood creatinine level was within normal ranges. Results for rheumatoid factor, antinuclear antibody, anti-cyclic citrullinated peptides, and human leukocyte antigen B27 were negative. Joint ultrasound suggested effusion in both the wrist joints and knee joints, synovial hyperplasia, and thickening of articular cartilage in both the knee joints as well as enlarged lymph nodes in the bilateral neck and groin. The patient was diagnosed with sJIA after infection, tumour, and other febrile diseases were ruled out, with a 27-joint Juvenile Arthritis Disease Activity Score (JADAS-27) of 56.5, indicating high disease activity. After obtaining parental consent, the patient was started on a regimen including TCZ (8

mg/kg/2 weeks, IV), ibuprofen suspension (4 ml/three times/day, orally), and methotrexate (7.5 mg/week, orally). After 1 day of treatment, the patient's fever subsided, and arthritis symptoms improved.

Thereafter, the patient received TCZ once every 2 weeks, and her condition continued to improve, with no recurrence of fever and steady improvement in her arthritic symptoms. However, repeat laboratory tests in September 2020 (after six infusions of TCZ) suggested that some cytokines remained at high levels(Tab.)and that the CRP level was elevated (14.1 mg/L, normal: < 6 mg/L). At this point, the patient was more resistant to repeated intravenous infusions, and her parents indicated that financial constraints might prevent them from continuing to afford TCZ treatment. We considered JAK inhibitors, which have the effect of inhibiting multiple cytokines including IL-6 and which have been shown to be effective in the treatment of adult rheumatoid arthritis (RA). Therefore, we chose the more economical and convenient tofacitinib (2.5 mg/twice/day) to replace the TCZ, whereas the other treatment regimens remained unchanged. After 5 months, the patient's arthritic symptoms disappeared, and the levels of acute phase reactants and cytokines decreased to normal ranges, indicating complete remission based on the JADAS-27(Fig. 1A and B and C).

The patient subsequently presented with mild swelling and pain in some joints in May 2021 due to upper respiratory tract infection. Laboratory tests revealed increased levels of acute phase reactants (ESR: 50 mm/h, CRP: 127 mg/L) and increased cytokine levels (IL-6: 39.29 pg/ml; sIL-2R: 1,714 pg/ml). However, after hospitalisation and one intravenous dose of TCZ and switch to oral tofacitinib, the patient's symptoms resolved rapidly, and her condition was stable at follow-up as of March 2022. Overall, the efficacy of sequential tofacitinib treatment after TCZ was remarkable in this patient.

Discussion

Abnormalities of the innate immune system in sJIA lead to activation of immunoreactive cells and release of pro-inflammatory ILs, such as IL-1, IL-6, IL-18, and TNF-α, and they tend to be innate auto-inflammatory diseases [3]. TCZ, a recombinant humanised anti-human IL-6 receptor monoclonal antibody, has been shown to be effective [4, 5] for treating sJIA. After the patient had had recurrent fever for 8 months ago, she was successfully treated with TCZ with remarkable outcomes and no adverse events.

Despite the positive efficacy of TCZ in our case of sJIA, the family considered that TCZ was expensive and rejected the long-term intravenous regimen. They wished to switch to a more economical, convenient, and effective drug for maintenance treatment. The patient's laboratory tests suggested abnormal levels of inflammatory markers, such as elevated levels of TNF-α, sIL-2R, IL-6, IL-4, IL-17, IL-10, and other cytokines, with IL-6 level particularly being significantly elevated[2]. In our previous clinical practice, we successfully treated one patient each with childhood scleritis and panniculitis with sequential tofacitinib, and both these patients were followed up for more than 2 years with stable disease outcomes; therefore, we tried to use tofacitinib as a sequential drug. As of the December 2021 follow-up, the patient in this study experienced slight recurrence after upper respiratory tract infection, but after one intravenous

infusion of TCZ treatment, sequential tofacitinib treatment was continued, and the disease was smoothly controlled with no adverse effects.

JAK inhibitors, including tofacitinib and baricitinib, that have been marketed in China have positive efficacy in the treatment of RA, but reports of their efficacy for JIA are limited. To date, to the best of our knowledge, this is the first case report of a sequential treatment using TCZ and JAK inhibitor for sJIA. In a previous case report, a patient with refractory sJIA was treated with a combination of NSAIDs, GC, methotrexate, and etanercept, and had a suboptimal outcome, with poor growth and multiple thoracic fractures. After 3 months of treatment with tofacitinib, systemic inflammation and arthritis resolved [6]. In addition, one patient with a diagnosis of polyarticular JIA (pJIA) at 10 years of age had polyarthritis persist into adulthood, and then, a diagnosis of collagenous colitis was obtained. The patient showed significant improvement in both arthritis and colitis symptoms with tofacitinib [7]. In contrast, another patient with pJIA with compromised joint function and growth, who had long responded poorly to multiple standard treatment regimens and who was dependent on GC, initiated treatment with tofacitinib and showed significant improvement in overall health. The patient discontinued systemic GC and was eventually diagnosed with comorbid Leri-Weill syndrome after the diagnosis was delayed due to recurrent joint swelling that obscured the imaging condition. By reviewing the relevant literature, we noted that only Miserocchi et al. [8] used baricitinib to treat three patients with JIA-associated uveitis, and the efficacy for uveitis was better than that for arthritis. Phase 3 clinical trials of tofacitinib (NCT 01500551, NCT 02592434, NCT01513902, and NCT 03000439) and baricitinib (NCT03773978, NCT04088396, NCT04088409, and NCT03773965) for JIA are available. Of these, a Phase 3 clinical trial conducted to validate tofacitinib efficacy, safety, tolerability, and study pharmacokinetics in sJIA patients is ongoing (NCT 03000439). A separate randomised, double-blind, placebo-controlled withdrawal study of baricitinib in patients aged 1–18 years with sJIA is in the recruitment phase (NCT04088396).

In addition, we found that the cytokine IL-6 level was significantly elevated in our patient before TCZ treatment, and the levels of various cytokines, including IL-6, increased further after 2 weeks of treatment with TCZ. On reviewing previous studies, Nishimoto et al. [9] has reported similar findings in RA patients. However, instead of a sustained increase, serum IL-6 levels after TCZ treatment remained stable between days 14 and 42. Further testing by the authors revealed no significant increase in IL-6 mRNA expression in peripheral blood cells before and after dosing in RA patients; therefore, it was hypothesised that the main reason for the elevation of serum IL-6 level was restriction of IL-6 clearance by TCZ binding to IL-6R, rather than an increase in endogenous production of IL-6 due to the negative feedback effect of inhibition. Our clinical observations were similar to the above findings, with our patient showing a transient elevation in the cytokine IL-6 level at the beginning phase of the disease and a gradual decrease to normal IL-6 level after further treatment. Further studies are needed regarding to corroborate the changes in cytokine levels after treatment with bDMARDs in patients with JIA.

Conclusions

The patient in our study was sequentially treated for sJIA with sequential TCZ and tofacitinib treatment, showing remarkable efficacy and resulting in the gradual normalisation of multiple cytokine expression levels. The sequential treatment using the IL-6 inhibitor and JAK inhibitor could be a new option for the treatment of sJIA.

Abbreviations

bDMARDs
Biological disease-modifying anti-rheumatic drugs
CRP
C-reactive protein
DMARDs
Disease-modifying anti-rheumatic drugs
ESR
Erythrocyte sedimentation rate
GC
Glucocorticoids
IL
Interleukin
JADAS-27
27-joint Juvenile Arthritis Disease Activity Score
JAK
Janus kinase
JIA
Juvenile idiopathic arthritis
NSAIDs
Nonsteroidal anti-inflammatory drugs
sJIA
Systemic juvenile idiopathic arthritis
T2T
Treat to target
TCZ
Tocilizumab

Declarations

- **Ethics approval and consent to participate:**The Ethics Committee of the second Clinical Medical College of Shanxi Medical University waived the need for formal approval in this case. Full consent for procedures described was obtained from the patient's parent or guardian

- **Consent for publication:** Written informed consent was obtained from the patient's parent or guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.
- **Availability of data and materials:** All data supporting our findings are contained within the manuscript.
- **Competing interests:**All authors have no conflicts of interest.
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- **Authors' contributions:** ZY acquired the data and wrote the manuscript. ZJX revised the manuscript. RJL examined the patient and made the diagnosis and critically revised the manuscript. All authors read and approved the final version of the manuscript.
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Tables

Table1

Follow-up of cytokine levels with tofacitinib treatment.

	TNF-α	sIL-2R	IL-6	IL-4	IL-2	IL-17	IL-10	IFN-γ
Jun. 28,2020	2.31	2810	287.95	2.38	1.58	1.01	4.52	2.54
Jul. 14,2020	2.96	1811	▯2500	8.76	1.1	35.36	8.67	4.29
Sep. 21,2020	1.48	2239	458.02	2.26	1.1	7.44	3.75	1.67
Jan. 21,2021	1.4	488	2.73	1.66	0.49	5.4	2.32	1.71
May. 15,2021	2.05	1714	39.29	1.21	0.61	9.34	5.87	4.45
Sep.30.2021	2.51	208	139.81	0.23	0.25	3.18	1.57	2.28
Dec.30.2021	1.23	392	243.36	0.931	1.30	0.03	2.59	2.57

Figures

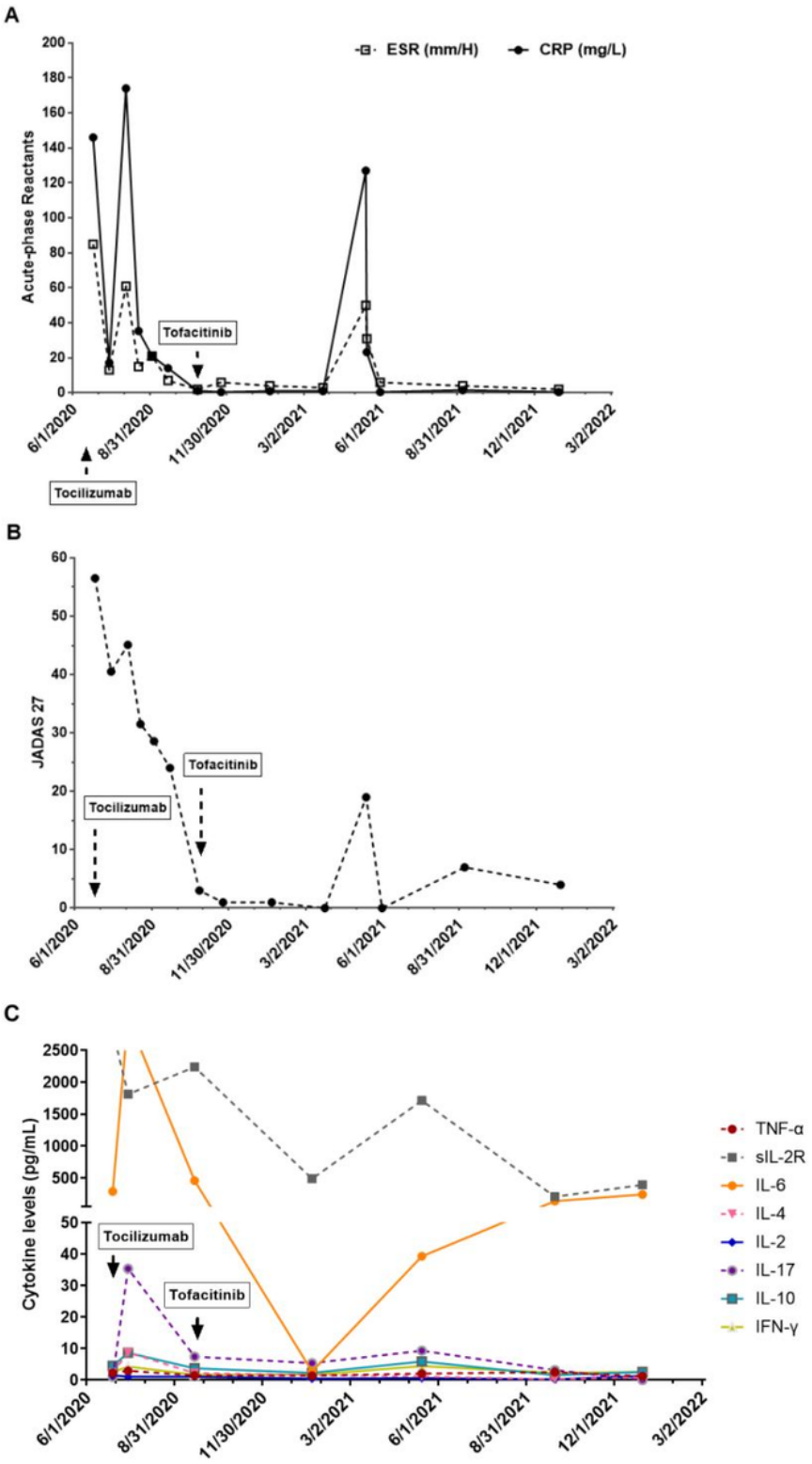

Figure 1

Follow-up of disease activity and acute-phase reactant levels with tofacitinib treatment. A, ESR and CRP levels before and after tofacitinib treatment. B, JADAS-27 before and after tofacitinib treatment. C, Cytokine levels before and after tofacitinib treatment.