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CASE REPORT

Sequential Tocilizumab and Tofacitinib Treatment for Systemic Juvenile Idiopathic Arthritis: a Case Report

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ABSTRACT

Systemic juvenile idiopathic arthritis (sJIA) is a complex and difficult to cure condition with high disability and mortality rates. Herein, we report the case of a patient with sJIA who was treated with sequential tocilizumab (TCZ) and tofacitinib treatment. The patient was a 4-year-old girl hospitalised with fever accompanied by multiple joint swelling and pain in June 2020. Laboratory tests revealed a white blood cell count of 15.3×10^9/L, platelet count of 676.8×10^9/L, haemoglobin of 91.8 g/L, serum ferritin level of 1103.8 U/L, erythrocyte sedimentation rate of 85.0 mm/h, C-reactive protein level of 146.0 g/L and interleukin (IL)-6 level of 288.0 pg/ml. Rheumatoid factor and autoantibodies test results were negative, and she was diagnosed with sJIA. The patient was started on a combination of ibuprofen, methotrexate and TCZ, and her fever decreased to the normal range without any recurrence. Painful joint swelling had resolved significantly at 3-month follow-up. Janus kinase (JAK) inhibitors inhibit the effects of several cytokines, particularly IL-6, and are economical and convenient. Therefore, we selected tofacitinib to replace TCZ in this case, while the other drugs remained unchanged. Arthritis symptoms disappeared gradually after 9-month follow-up. In May 2021, the patient was hospitalised owing to a slight recurrence of the upper respiratory tract infection. She was administered one intravenous infusion of TCZ along with a switch to oral tofacitinib, which quickly relieved the symptoms. In March 2022, the patient's condition was stable. The curative effect of sequential TCZ and tofacitinib treatment was remarkable. IL-6 inhibitors sequential to JAK inhibitors could be a new option in the treatment of systemic juvenile idiopathic joints.

Keywords: Systemic juvenile idiopathic arthritis; Tocilizumab; Tofacitinib; Sequential treatment

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Key Summary Points

Systemic juvenile idiopathic arthritis is the most serious subtype of juvenile idiopathic arthritis.

We describe a clinical case of systemic juvenile idiopathic arthritis in a 4-year-old girl with fever accompanied by multiple joint swelling and pain. Systemic juvenile idiopathic arthritis was diagnosed after exclusion of infections, haematologic neoplasms and other febrile illnesses.

The girl was sequentially treated with sequential tocilizumab and tofacitinib, which showed remarkable efficacy leading to the gradual normalisation of multiple cytokine expression levels.

The sequential treatment using the interleukin-6 and Janus kinase inhibitors could be a new treatment option for systemic juvenile idiopathic arthritis.

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is the most severe subtype of juvenile idiopathic arthritis (JIA). sJIA is distinct from other forms of JIA, and is associated with significant systemic inflammatory features, such as fever and rash, in addition to arthritic manifestations, while intrinsic immune abnormalities and autoantibodies are usually absent. Treatment options for sJIA include use of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological disease-modifying anti-rheumatic drugs (bDMARDs). However, challenges in managing and controlling sJIA are still noted in few patients with systemic symptoms and arthritic manifestations, or in those who present with serious drug side effects or complications. bDMARDs should be administered rapidly when patients fail to respond or respond poorly to conventional treatments [1]. bDMARDs are effective in reducing the morbidity and mortality of rheumatic diseases in children [2]. In recent years, the treat to target (T2T) model in paediatric rheumatic diseases has been gradually developed, which aims to control symptoms and signs, prevent structural damage, avoid co-morbidity and drug toxicity, optimise function, growth and development, and improve disease-related quality of life and social participation [3]. The use of bDMARDs, such as interleukin (IL)-1 or IL-6 inhibitors, is extremely important in the realisation of T2T for patients with sJIA. The IL-6 receptor antagonist tocilizumab (TCZ) and IL-1 inhibitor anakinra have been approved by the European Medicines Agency and the US Food and Drug Administration (FDA) for the treatment of sJIA. However, only the intravenous form of TCZ has been approved for the treatment of sJIA in China. Moreover, patients often require alternative treatment options owing 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 [4]. In September 2020, the FDA approved the use of tofacitinib to treat patients with polyarticular-course juvenile idiopathic arthritis (pcJIA) $\geq$ 2 years old. Subsequently, in August 2021, the European Commission approved its use for patients with polyarticular juvenile idiopathic arthritis (pJIA) or juvenile psoriatic arthritis, and on November 9, 2021, the results of the phase 3 clinical trial of tofacitinib in the treatment of JIA were published in *The Lancet*. The results showed that tofacitinib can effectively reduce disease recurrence, prolong the relapse free time, and improve the treatment response rate of pcJIA [5]. However, in the recently published trials, the effects in the sJIA subgroup did not reveal any statistical significance. In a previous case report, a patient with refractory sJIA was treated with a combination of NSAIDs, GCs, methotrexate and etanercept, achieving a suboptimal outcome, with poor growth and multiple thoracic

fractures. However, after 3 months of treatment with tofacitinib, systemic inflammation and arthritis were resolved [6].

Herein, we report the case of a 4-year-old patient with sJIA with significant systemic and arthritis symptoms in which the effects of TCZ sequential tofacitinib were significant. The potential benefits of tofacitinib include its oral route of administration and low cost. We hope to optimise the diagnosis and treatment plan of patients with sJIA, to allow patients to benefit as much as possible both socially and economically, and provide a practical basis for an alternative treatment plan involving IL-6 inhibitors in the future.

ETHICS DECLARATIONS

The present case report was written according to the CAse REport (CARE) guidelines. The Ethics Committee of the Second Hospital of Shanxi Medical University has approved the publication and waived the informed consent application of this case report. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

RESULTS

In June 2020, a 4-year-old girl (height 110 cm, weight 20 kg) visited our hospital presenting with recurrent fever accompanied by multiple joint swelling and pain (Fig. 1).

Eight months earlier, the patient had developed chills and fever, with a body temperature up to 39.5 °C. The initial diagnosis of the patient was not clear. She experienced fever which subsided after the administration of intermittent oral dexamethasone tablets but recurred on discontinuing 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 reported primarily 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 longer than 4 h. The patient's daily life was severely affected; she was unable to walk, and required significant support from others. From February to May 2020, the patient visited several hospitals, all of which failed to diagnose the disease; she received various treatments from these hospitals, including ibuprofen suspension (3 ml three times per day, orally), dexamethasone injection (3 mg, intramuscularly, once), Chinese herbal medicine bath (the specific ingredients was unknown) and etanercept (12.5 mg, subcutaneously, twice). However, her fever and arthritis symptoms showed little improvement. In June 2020, the patient was referred to the Children's Hospital of the Capital Institute of Pediatrics. Laboratory test results suggested a negative purified protein derivative

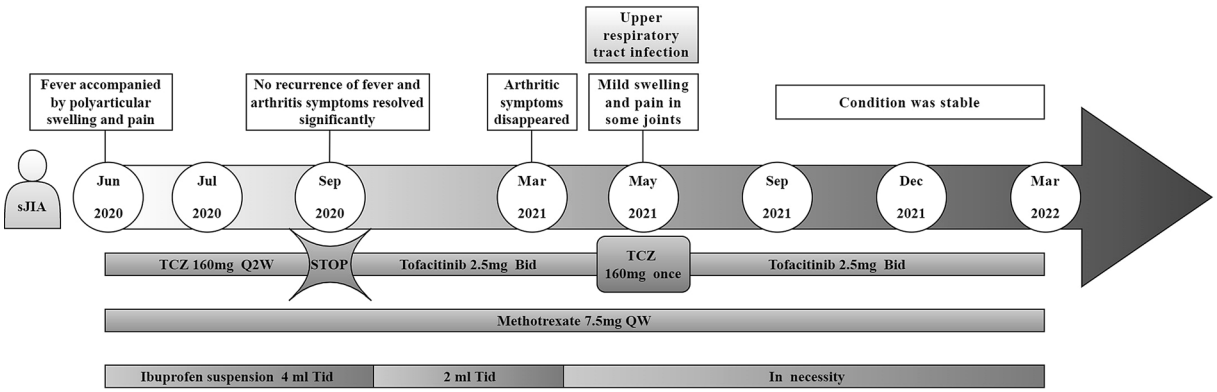

Fig. 1 Timeline of the present case report

test, T-cell spot test of tuberculosis infection, anti-cyclic citrullinated polypeptide and human leucocyte antigen B27. Enhanced magnetic resonance imaging of the left knee revealed effusion and synovitis of the left knee. Her family medical history was unremarkable. The patient did not undergo any further therapeutic intervention according to the physician's advice.

As the symptoms continued, the patient presented to our hospital, where physical examination revealed swelling and tenderness in the interphalangeal joints, metacarpophalangeal joints, wrists, elbows, knees, ankles and metatarsophalangeal joints. She was uncooperative with Patrick's test, and complete blood count revealed mild microcytic anaemia (haemoglobin 91.8 g/L, mean corpuscular volume 68.9 fL), increased white blood cells (15.3×10^9/L), neutrophils (7.9×10^9/L), lymphocytes (5.5×10^9/L), monocytes (1.7×10^9/L), eosinophilic granulocytes (0.1×10^9/L), basophils (0.1×10^9/L) and thrombocytosis (676.8×10^9/L) along with a serum ferritin level of 1,103.8 U/L, erythrocyte sedimentation rate (ESR) of 85.0 mm/h, C-reactive protein (CRP) level of 146.0 g/L, significantly elevated cytokine IL-6 level of 288.0 pg/ml, alanine transaminase level of 53.3 U/L and albumin level of 26.0 g/L. Test results for rheumatoid factor, anti-nuclear antibody, anti-cyclic citrullinated peptides and human leucocyte antigen B27 were negative. Ultrasound suggested effusion in both the wrist joints and knee joints, synovial hyperplasia and thickening of the articular cartilage in both the knee joints, as well as enlarged lymph nodes in the bilateral neck and groin regions. She was diagnosed with sJIA after exclusion of infections (including streptococci, tuberculosis, respiratory pathogens and Epstein–Barr virus infection) and other febrile illnesses (including Kawasaki disease and systemic lupus erythematosus), as well as after undergoing a haematological consultation to exclude haematologic neoplasms. The patient's 27-joint Juvenile Arthritis Disease Activity Score (JADAS-27) was 56.5, indicating high disease activity. After obtaining parental consent, the patient was started on a regimen comprising TCZ (8.0 mg/kg every 2 weeks, intravenously), ibuprofen suspension (4 ml three times per day, orally) and methotrexate (7.5 mg per week, orally). After 1 day of treatment, the patient's fever subsided and her 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 test results obtained in September 2020 (after six infusions of TCZ) suggested the presence of certain cytokines at high levels (Table 1) and an elevated CRP level (14.1 mg/L, normal: < 6.0 mg/L). At this point, the patient was more resistant to repeated

Table 1 Follow-up of cytokine levels before and after treatment

Cytokine (pg/ml)	TNF-α	sIL-2R	IL-6	IL-4	IL-2	IL-17	IL-10	IFN-γ
28 June 2020	2.3	2810.0	288.0	2.4	1.6	1.0	4.5	2.5
14 July 2020	3.0	1811.0	> 2500.0	8.8	1.1	35.4	8.7	4.3
21 September 2020	1.5	2239.0	458.0	2.3	1.1	7.4	3.8	1.7
21 January 2021	1.4	488.0	2.7	1.7	0.5	5.4	2.3	1.7
15 May 2021	2.1	1714.0	39.3	1.2	0.6	9.3	5.9	4.5
30 September 2021	2.5	208.0	139.8	0.2	0.3	3.2	1.6	2.3
30 December 2021	1.2	392.0	243.4	0.9	1.3	0.0	2.6	2.6
10 February 2022	5.5	523.0	343.4	4.8	3.3	13.3	6.7	6.7

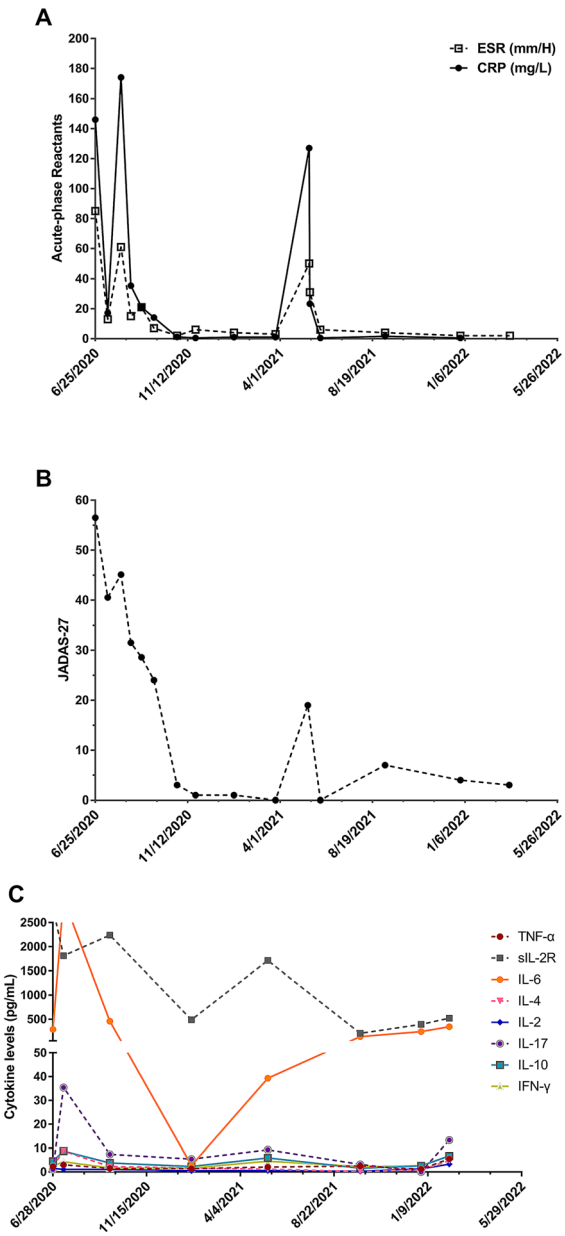

Fig. 2 Follow-up of disease activity and acute-phase reactant levels. ESR and CRP levels before and after treatment (**A**); JADAS-27 before and after treatment (**B**); cytokine levels before and after treatment (**C**)

intravenous infusions, and her parents indicated that financial constraints may prevent them from continuing TCZ treatment. We considered JAK inhibitors, which function to inhibit multiple cytokines, including IL-6, and are effective in the treatment of adult rheumatoid arthritis (RA). Therefore, we chose the more economical and convenient drug, tofacitinib (2.5 mg twice per day), to replace 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. 2A–C).

The patient subsequently presented with mild swelling and pain in some joints in May 2021 following an upper respiratory tract infection. Laboratory tests revealed increased levels of acute phase reactants (ESR 50.0 mm/h, CRP 127.0 mg/L) and increased cytokine levels [IL-6 39.3 pg/ml, soluble interleukin-2 receptor (sIL-2R) 1714.0 pg/ml]. However, the patient's symptoms resolved rapidly after hospitalisation and a single intravenous dose of TCZ along with a switch to oral tofacitinib, and her condition has remained stable at follow-up as of March 2022. Overall, the efficacy of sequential tofacitinib treatment provided after the use of TCZ was remarkable in the present patient.

DISCUSSION

Abnormalities of the innate immune system in patients with sJIA lead to the activation of their immunoreactive cells and a release of pro-inflammatory ILs, including IL-1, IL-6, IL-18 and tumour necrosis factor (TNF)-α. sJIA may be considered an autoinflammatory disorder [7]. TCZ, a recombinant humanised anti-human IL-6 receptor monoclonal antibody, is an effective treatment for sJIA [8, 9]. In our case report, after a history of recurrent fever for 8 months, the patient was successfully treated with TCZ with remarkable outcomes and no adverse events.

Despite the positive efficacy of TCZ in this case of sJIA, the family considered that TCZ was expensive and rejected undergoing a long-term intravenous regimen, expressing a desire to switch to a more economical, convenient and effective drug for maintenance treatment. The patient's laboratory test results revealed

abnormal levels of inflammatory markers, including elevated levels of TNF-α, sIL-2R, IL-6, IL-4, IL-17, IL-10 and other cytokines, with especially the IL-6 level being significantly elevated. In our previous clinical practice, we successfully treated one patient each with childhood scleritis and panniculitis with sequential tofacitinib, both of whom were followed up for more than 2 years and demonstrated stable disease outcomes; therefore, we attempted tofacitinib as a sequential drug in this patient as well. As of March 2022, our patient experienced a slight recurrence following upper respiratory tract infection; however, after one intravenous infusion of TCZ treatment, sequential tofacitinib treatment was continued, and the disease was effectively controlled with no adverse effects.

JAK inhibitors, including tofacitinib and baricitinib, have been marketed in China and have proven to be effective in the treatment of RA; however, reports of their efficacy for sJIA are limited. To the best of our knowledge, this is the first case report of sequential treatment using TCZ and a JAK inhibitor for sJIA. In a previous similar report, one patient with a diagnosis of pJIA at 10 years of age had polyarthritis that persisted through adulthood, after which a diagnosis of collagenous colitis was obtained; this patient showed significant improvement in both arthritis and colitis symptoms on treatment with tofacitinib [10]. Another patient with pJIA and compromised joint function and growth, who had long responded poorly to multiple standard treatment regimens and was dependent on GC, received treatment with tofacitinib, achieving a significant improvement in overall health. The patient discontinued systemic GC and was eventually diagnosed with comorbid Léri–Weill syndrome after the diagnosis was delayed owing to recurrent joint swelling that obscured the imaging condition [11]. On reviewing the relevant literature, we noted that only Miserocchi et al. [12] used baricitinib to treat three patients with JIA-associated uveitis, and its efficacy for uveitis was better than that for arthritis. Phase 3 clinical trials of tofacitinib (NCT01500551, NCT02592434 and NCT 03000439) and baricitinib (NCT03773978, NCT04088396, NCT04088409 and NCT03773965) for JIA are available. Of these, the results of a phase 3 randomised withdrawal of tofacitinib for the treatment of pcJIA have been published (NCT02592434), and Ruperton et al. [5] reported that tofacitinib was effective in the treatment of pcJIA, with a significant benefit of oral administration. Moreover, the safety profiles were consistent with those reported in the treatment of RA in adults, with no potential safety risks identified for tofacitinib in the treatment of pcJIA. A Phase 3 clinical trial conducted to validate tofacitinib efficacy, safety and tolerability and study pharmacokinetics in patients with sJIA is currently ongoing (NCT03000439). Furthermore, 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, we found that Nishimoto et al. [13] reported similar findings in patients with RA. 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 primary reason for the elevation of serum IL-6 level was the restriction of IL-6 clearance by TCZ binding to IL-6 receptor, rather than an increase in the endogenous production of IL-6 due to the negative feedback effect of inhibition. Our clinical observations were consistent with the above findings, as our patients demonstrated a transient elevation in cytokine IL-6 levels at the beginning of the disease, with a gradual decrease to normal IL-6 levels after further treatment. Further studies are required to corroborate the changes in cytokine levels following treatment with bDMARDs in patients with JIA.

CONCLUSIONS

In this report, we presented the case of a 4-year-old girl diagnosed with sJIA with significant systemic and arthritic symptoms. She was treated with a combination of ibuprofen, methotrexate and TCZ, which lead to a relief of the acute systemic symptoms. Arthritis symptoms disappeared after tofacitinib was administered instead of TCZ, and inflammatory indicators, as well as multiple cytokine levels, were gradually normalised. We recognise the limitations of the retrospective nature in this study; individual diagnosis and treatment experience are not universal, and there is not enough follow-up time. However, we can conclude that tofacitinib sequential to TCZ can be effective in this study. In the future, use of IL-6 inhibitors sequential to the use of JAK inhibitors could be a new option for the treatment of this disease.

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Author Contributions. Ye Zhang acquired the data and wrote the manuscript. Jinxiu Zhang revised the manuscript. Jinli Ru examined the patient, made the diagnosis and critically revised the manuscript. All authors have read and approved the final version of the manuscript.

Disclosures. Ye Zhang, Jinli Ru and Jinxiu Zhang declare that they have no competing interests.

Compliance with Ethics Guidelines. The guardian of patient has provided consent to publish this report. The Ethics Committee of the Second Hospital of Shanxi Medical University has approved the publication and waived the informed consent application of this case report. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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