Problems to Consider Before Determining the Regimen of the Treatment for Juvenile Systemic Sclerosis Treatment: A Case Report Where Tocilizumab Monotherapy Succeeded Efficiently and Safely

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ABSTRACT: Juvenile systemic sclerosis (SSc) is a rare condition that results in various disorders, including growth retardation and learning disabilities in addition to impaired quality of life due to fibrosis and microvascular disorders in multiple organs. Recently, efficacies of immunosuppressants such as cyclophosphamide and mycophenolate mofetil, as well as biological agents, have been reported in adult patients with SSc. However, there has been no consensus in the treatment of juvenile SSc due to its rarity and the fact that skin sclerosis may be self-limiting in some patients. Here, we present a case of 13-year-onset SSc with growth retardation and learning disabilities, in addition to skin sclerosis, interstitial lung disease, and possible myocardial fibrosis that was successfully treated with tocilizumab monotherapy without remarkable adverse reactions. As careful case-by-case management of patient's growth and education along with standard treatment is needed, the documentation of such case is important for the evaluation of the efficient and safe therapy for juvenile SSc.

KEYWORDS: Juvenile, systemic sclerosis, growth, fibrosis, tocilizumab

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Introduction

Systemic sclerosis (SSc) is characterized by inflammation, vasculopathy, and fibrosis not only in the skin but in various organs such as the lung, heart, digestive system, kidney, and joints, which impair the prognosis and the quality of life (QOL). The SSc mainly occurs in those in 50s to 60s, with childhood-onset SSc having been reported to comprise approximately 10% of total SSc cases with a mean age of onset at 8.8 years.[1] In these cases of childhood-onset, diffuse cutaneous sclerosis is more common than limited cutaneous one. Clinical trials of SSc in children have been difficult due to its rarity and the fact that skin sclerosis may be self-limiting in some patients. Hence, treatment for juvenile SSc (jSSc) has been usually determined according to previous studies of adult patients. In addition, there are special problems, including growth retardation, educational, and psychological disorders, to solve.[2] Recently, several scoring methods for disease activity in jSSc have been proposed and jSSc severity score (J4S)[3] has been reported to be better than Medsger et al[4] severity score for adults with SSc. Here, we present a case of jSSc, showing progressively worsened skin sclerosis as well as growth retardation, interstitial lung disease (ILD), and possible cardiomyopathy that was successfully treated with anti-interleukin (IL)-6-receptor monoclonal antibody, tocilizumab (TCZ). Because there has been no consensus on the treatment for jSSc, we studied what problems to consider before determining the regimen of the treatment through this case.

Case Report

A 13-year-old Japanese female was healthy until 3 years before, when she came to feel coldness and morning stiffness in her hands, followed by Raynaud's= phenomenon every winter. Thereafter, cyanosis in the fingers began to occur along with skin sclerosis and she visited our clinic. On examination, her height, body weight, and body mass index (BMI) were 138.0 cm, 30.4 kg, and 16 (<3rd, <3rd, and <10th percentile, respectively, compared with those of the average of Japanese female of the same age). Blood pressure was 86/46 mmHg and pulse rate was 119/min. There was skin sclerosis in the extremities, chest, and abdominal walls and the face (modified Rodnan skin score [mRSS] was 21/51) and the lingual frenum was shortened. There was narrowing of fingertips, the left second distal interphalangeal joint was flexed, and there was a digital ulcer on the fingertip of the left thumb and were multiple scars on the extensor side of bilateral interphalangeal and knee joints (Figure 1A). Nailfold capillaroscopy revealed giant capillaries, hemorrhage, and moderate loss of capillaries.

No heart murmurs nor rales were heard in the chest. Laboratory examination showed the serum antinuclear antibody of diffuse and speckled patterns, anti-topoisomerase I antibody was positive, and the serum level of IL-6 was increased (5.5 pg/mL; normal < 4.0). Blood concentrations of Krebs von den Lungen–6 (KL-6), a biomarker for ILD, and troponin I were slightly elevated (899 U/mL; normal < 500 and 0.052 ng/mL; normal < 0.026, respectively) and chest radiograph showed a slight ground-glass appearance in the middle and lower lung fields although high-resolution computed tomography (HRCT) of the chest was not performed due to claustrophobia. Electrocardiography showed multifocal ventricular premature contractions and echocardiography revealed hypokinesis of the basal interventricular septum and posterior wall of

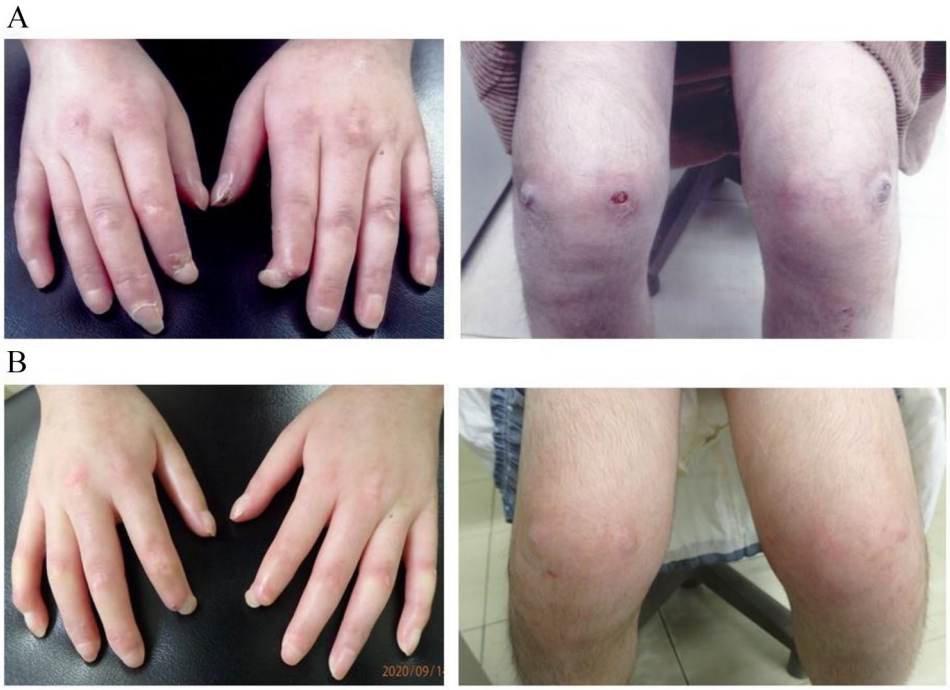

Figure 1. Photograph of the hands and legs. (A) Before tocilizumab administration, there was narrowing of the fingertips and the left second distal interphalangeal joint showed fixed flexion and multiple scars on the extensor side of bilateral interphalangeal and knee joints; there is a digital ulcer on the tip of the left thumb. (B) Nine months after tocilizumab administration, skin sclerosis showed improvement and fingertip erosion disappeared.

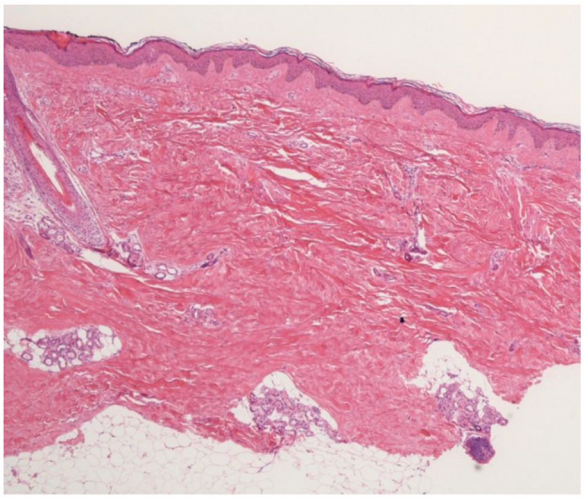

Figure 2. Pathological findings of the skin (stained with hematoxylin-eosin; 40×).
Skin specimen from the forehand shows thinned epidermis and increased collagen fibers with atrophied dermal appendages.

the left ventricle, and the ejection fraction (EF; calculated by Teichholz formula) was reduced to 50%, while tricuspid pressure gradient was not increased and there was no enlargement of the right ventricle. Pathological examination of the skin specimen from her forehand showed thinned epidermis and increased collagen fibers with atrophied dermal appendages (Figure 2).

Under diagnosis of diffuse cutaneous systemic sclerosis, prednisolone (PSL; 10 mg/d) and an oral prostaglandin E1 analog, limaprost alfadex, were started, followed by an endothelin receptor antagonist, bosentan. During the initial 1½ years, her skin sclerosis slightly improved (mRSS reduced to 15), but this effect did not last long. As she frequently suffered from palpitation, fainting, and dyspnea on exertion, becoming unable to attend school, she took a correspondence education, and limaprost alfadex and bosentan were ceased. During the next 6 months, her skin sclerosis began to gradually progress again and mRSS reached above 40, reflux esophagitis often occurred, and she came to suffer from depression. On the contrary, the dose of PSL was tapered to 1 mg/d because of amenorrhea. Thereafter, treatment strategy was discussed and TCZ (162 mg subcutaneously once every 2 weeks) was prescribed under approval by the ethics committee of our institute (committee ID: RH30-13) and informed consent from the patient and her parents, including payment of the medical costs. A few weeks after beginning of TCZ administration, skin sclerosis began to improve and mRSS reduced to 24 and fingertip erosion disappeared after 9 months of administration (Figure 1B), when it was ceased due to economical reason (Figure 3A). The mRSS continued to decrease to 14 after cessation of TCZ and stayed at the similar values over a year. In addition, serum KL-6 level that had been slightly elevated before TCZ administration showed a tendency to decrease (Figure 3B). In addition, serum troponin level reduced, although the findings of echocardiography did not change remarkably (Figure 3C). Although her exact initial disease severity score could not be calculated because of the missing data of spirometry and HRCT, it was presumed that possible ILD and cardiomyopathy might have improved judging from the reduction of the serum KL-6 and troponin I levels, respectively. Furthermore, Health Assessment

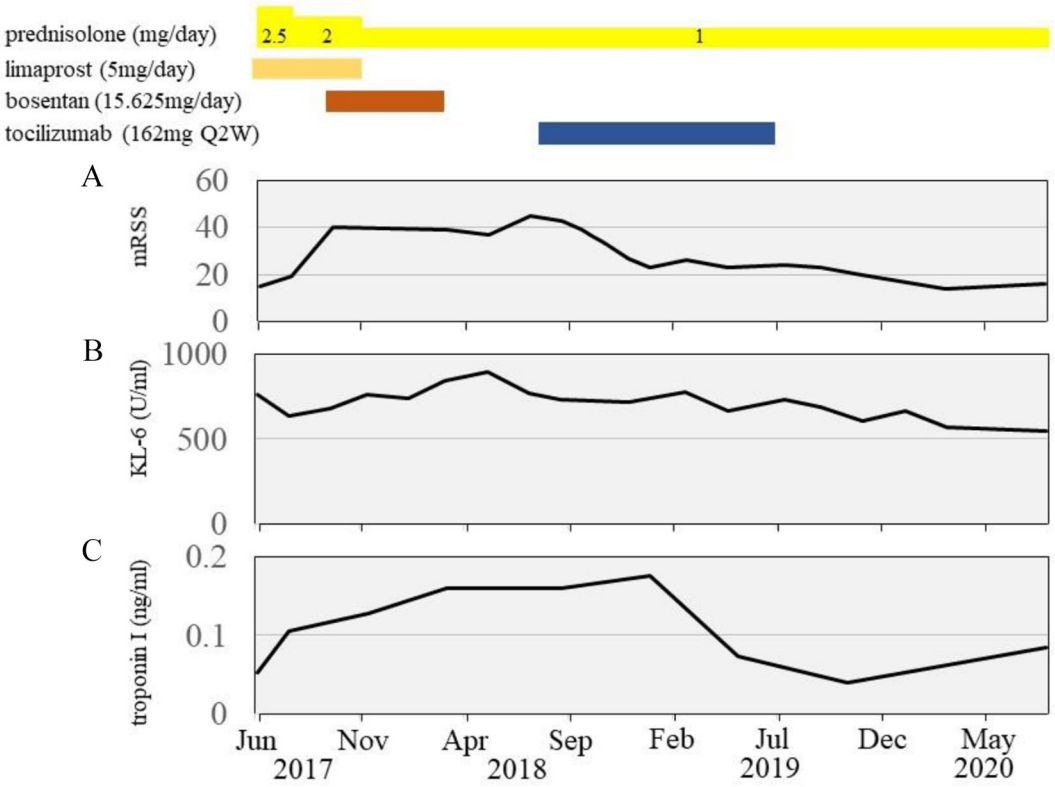

Figure 3. Clinical course. Changes in the (A) mRSS score, (B) the serum level of KL-6, and (C) the serum level of troponin I.
KL-6 indicates Krebs von den Lungen–6; mRSS, modified Rodnan skin score.

Questionnaire–Disability Index (HAQ-DI) gradually decreased from 2.25 at the beginning to 1.25 after 9 months of treatment, and finally to 1.13 one year after the end of the TCZ treatment.

Discussion

In SSc, Raynaud phenomenon usually precedes, followed by skin sclerosis, while physical function and mental status of the patient are impaired as disease progresses. Digital ulcer or necrosis frequently occurs due to disorder of microcirculation, in which abnormalities related to vasoactive mediators such as endothelin-1, prostaglandins, angiotensin II, and nitrogen oxide have been thought to be involved. In this case, an endothelin receptor antagonist and a prostaglandin analog were used for digital ulcers, but they had to be withdrawn because of an adverse reaction of hypotension.

Thus far, various drugs to improve immune disorders and fibrosis have been used,[5] and recently, SHARE initiative has provided a recommendation based on expert opinion[6] that recommends corticosteroids, methotrexate (MTX), mycophenolate (MMF), or cyclophosphamide (CY), while hematopoietic stem-cell transplantation (HSCT) has been also recommended. However, from the experience of treating Japanese patients with rheumatoid arthritis, adverse reactions by MTX such as interstitial pneumonitis, liver injury, and lymphoproliferative disease tend to be more frequent in Japanese patients compared with other races[7,8] and coexisting ILD makes it difficult to use this agent. On the contrary, clinical trials have shown the effectiveness of CY in SSc, but these focused on patients older than 17 years of age, while some are retrospective studies or without control population. Apart from this, various adverse reactions such as bone marrow suppression, infertility, malignancy, myocardial injury, and growth retardation have been reported in addition to the risk of infection.[9] There have been several reports about the effects of MMF. Although most of these have agreed on its efficacy on SSc, especially on the skin sclerosis and ILD,[9] some have reported no difference between MMF and CY[10,11] and the safety data of MMF in children are not enough. Regarding calcineurin inhibitors, some studies have argued the efficacy of CyA, while adverse reactions such as hypertension and renal impairment were frequent and there were no remarkable effects on the cardiac disease or ILD.[12] Furthermore, transplantation-related death and relapse during HSCT could not be excluded.[13] Therefore, the use of these immunosuppressive agents is thought to be limited in this case.

During the past few years, effectiveness of certain biologics in SSc has been reported: anti-BLyS (B lymphocyte stimulator) monoclonal antibody (mAb) (belimumab),[14] recombinant CTLA4-Ig (abatacept),[15] anti-TGF (transforming growth factor)-β mAb (fresolimumab),[16] anti-CD20 mAb (rituximab),[17,18] and anti-IL-6 receptor mAb (TCZ).[19-21] Belimumab has been reported to be effective in a small pilot study with an increased risk of infection and mood disorder, while abatacept has also been shown to be effective in a small-population study with increased risk of infection. A small study

has reported the effectiveness of fresolimumab, but there was at least an adverse reaction of anemia. A number of studies have reported the effectiveness of rituximab in SSc, but they found a risk of bone marrow suppression and mucocutaneous reactions as well as infection. On the contrary, there have been several reports on the usefulness of TCZ in skin sclerosis and pulmonary fibrosis in SSc.[22,23] Furthermore, TCZ has been already used in systemic type of juvenile idiopathic arthritis, as well as rheumatoid arthritis, and Takayasu arteritis which often occurs in patients younger than other connective tissue diseases. Therefore, TCZ seems comparatively safe for children.

While growth retardation in this case might be associated with the pathogenesis of jSSc, total assessment of the severity of jSSc before the treatment was done by 6 components of J4S. For the general component, reduction in BMI was severe although hemoglobin value was normal. Both of vascular and skin components were thought to be severe, gastrointestinal (GI) tract component was moderate, and the progression of the skin sclerosis seemed very rapid before the treatment with TCZ. For the respiratory component, mild to moderate severity was suspected because there was a ground-glass appearance in the lung field with slightly elevated level of the serum KL-6 that suggests the existence of ILD. For the cardiac component, elevation of troponin I level, arrhythmia, and hypokinesis of the ventricular wall might have suggested the existence of possible myocardial fibrosis. Unfortunately, pulmonary function test, HRCT, and gadolinium-enhanced magnetic resonance imaging (MRI) of the cardiac muscle were not performed as the patient did not consent to these tests due to claustrophobia. Therefore, assessment of the disease activity by J4S was not enough because there was a discrepancy between BMI and hemoglobin values, quantitative assessment of ILD was lacking, and existence of myocardial fibrosis was a matter of speculation. However, we decided to choose TCZ for this case from a comprehensive assessment. Within a few weeks after the start of the treatment, progression of skin sclerosis seemed to stop, mRSS score gradually reduced thereafter, and this effect continued for more than a year even after discontinuation of the drug. It is known that skin sclerosis may improve naturally in the course of this disease. However, she began to manifest SSc at the age of 10 and that skin sclerosis had been worsening progressively until TCZ began, although it had improved transiently with the use of corticosteroid. Therefore, this effect might be ascribed to the action of TCZ. Furthermore, improvement of possible ILD and myocardial fibrosis judging from the serum levels of KL-6 and troponin I might be due to the improvement of tissue fibrosis by the action of TCZ. Furthermore, it is important to note that there was an improvement in the patient's QOL after the TCZ administration while she felt more physically active and motivated to study.

Conclusions

A case of jSSc was presented which was efficiently and safely treated with TCZ monotherapy and TCZ was thought to be 1 of the candidates for the treatment of jSSc. Given that there has been no consensus of the regimen for the treatment of jSSc, it was thought important to carefully assess the patients' status specific to children, including educational and psychological problems in addition to multiple organ disorders due to tissue fibrosis. Overall, accumulation of these cases seemed to be essential.

Author Contributions

MF is the corresponding author responsible for the writing of this article. MF and KK managed the patient and approved the final manuscript.

Informed Consent

The authors obtained written consent from the patient for the publication of this case report and any accompanying images.

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