Systemic Sclerosis

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Contributor: Yoshihito Shima

Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology. SSc causes damage to the skin and various organs including the lungs, heart, and digestive tract, but the extent of the damage varies from patient to patient. The pathology of SSc includes ischemia, inflammation, and fibrosis, but the degree of progression varies from case to case. Many cytokines have been reported to be involved in the pathogenesis of SSc. For example, interleukin-6 is associated with inflammation, and transforming growth factor-β and interleukin-13 are associated with fibrosis. Therapeutic methods to control these cytokines have been proposed; however, which cytokines have a dominant role in SSc might differ depending on the stage of disease progression and the extent of visceral lesions. Therefore, it is necessary to consider the disease state of the patient when an anti-cytokine therapy is conducted.

Keywords: systemic sclerosis ; interleukin-6 ; interleukin-13 ; tocilizumab

1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by abnormal peripheral vessels and fibrotic changes in the skin and visceral organs. Two types of SSc can be distinguished by the spread of the sclerotic skin area. Systemic skin involvement is referred to as diffuse cutaneous SSc (dcSSc) and sclerosis limited to the fingers, hands, and forearms is known as limited cutaneous SSc (lcSSc) [1]. Both types exhibit fibrotic changes in visceral organs, especially the esophagus, lungs, and heart. Most patients with dcSSc are positive for the anti-topoisomerase-1 antibody (anti-Scl-70 antibody) or the anti-RNA polymerase III antibody, and most lcSSc patients have an anti-centromere antibody present in their sera [2][3]. The clinical symptoms of SSc include vascular damage, inflammation, and fibrosis. The etiology of SSc has not been identified, but many cytokines and chemokines associated with its pathological state have been reported. In particular, the proinflammatory cytokine interleukin (IL)-6, and the fibrosis-related cytokine IL-13 and transforming growth factor (TGF)-β have been reported to be involved in the pathogenesis of SSc, and have been considered as targets for anti-cytokine therapy.

2. Anti-Cytokine Therapy

Various anti-cytokine therapies with biologics have been investigated. dcSSc patients were treated with CAT-192, a neutralizing anti-TGF-β antibody [4] at three different doses: 0.5, 5, and 10 mg/kg. After 6 months of observation, no significant decrease in skin score was observed in the active treatment group although the skin score tended to be decreased in patients with longer disease duration.

Anti-IL-6 therapies have also been examined. Tocilizumab (TCZ), a monoclonal antibody against human IL-6 receptor (IL-6R), was developed by Chugai Pharmaceutical Co., Ltd. in Japan, and is now used as a therapy for Castleman disease, Takayasu arteritis, giant cell arteritis, idiopathic juvenile arthritis, and rheumatoid arthritis. TCZ inhibits the binding of IL-6 to IL-6R. Cells expressing IL-6R are limited to hepatocytes, but its signal transduction molecule gp130 is expressed in most human cells [5]. The soluble form of IL-6R is present in serum and can generate an inflammatory signal via gp130 when it binds to IL-6. Therefore, inhibiting the action of IL-6R is a reasonable strategy to block IL-6 function. We reported that SSc cases treated with TCZ had decreased skin score and the skin hardness evaluated by Vesmeter, a device that measures the hardness, elasticity, and viscosity of skin [6]. On the basis of these findings, a phase II randomized controlled trial (faSScinate study) was conducted in 2012 [7]. The primary end-point was modified Rodnan Skin Score (mRSS), and the TCZ patients showed a tendency toward a greater reduction of mRSS, and they also showed smaller reductions of forced vital lung capacity than those of the placebo group. To verify these results, a new expanded multicenter trial in 27 countries (focuSSced study) had conducted in 2017. It was expected that the decrease in mRSS would become clear, but the variability of change in mRSS was getting widely, and the results seen in the faSScinate study have been blurred [8]. In the focuSSced study, the entry criteria were patients within 60 months of onset, based on the understanding that the inflammation stage of SSc is early in the disease course. Although the decreased skin scores

in the TCZ group did not reach statistical significance compared with the placebo group, the pulmonary function test demonstrated that the average of the decrease of forced vital lung capacity in the TCZ group was smaller than that of the placebo group. TCZ is now approved by the United States Food and Drug Administration to treat lung involvement in SSc patients.

Recently, a clinical trial of romilkimab, a bispecific immunoglobulin G4 that neutralizes IL-4 and IL-13, demonstrated changes in the mRSS of dcSSc patients. At 24 weeks of observation, the romilkimab group had a significantly lower mRSS than the placebo group [9]. As described above, since IL-6 play a pathological role in inflammation and IL-13 play a role in fibrotic changes, anti-IL-6 therapy may be successful in patients with a short disease duration and anti-IL-13 therapy might be successful in patients with advanced-stage.

3. Evaluation of Anti-Cytokine Therapy

It is expected that various anti-cytokine therapies will be approved in the future, but there are many problems to overcome before their practical use. For SSc, it will be necessary to decide the target stage and the target involved organs. In the focuSSced study, the entry criteria were patients within 60 months of onset, based on the understanding that the inflammation stage of SSc is early in the disease. A disadvantage of large-scale trials targeting SSc is that the condition of SSc patients differs depending on their disease stage. IL-6 and TNF-α have important roles in the early- and late-stage pathogenesis of rheumatoid arthritis. However, factors involved in the pathogenesis of SSc are thought to change depending on the stage of disease progression. Furthermore, the speed of disease progression caries in each patient. When the patients with SSc received TCZ, the degree of mRSS reduction correlated with a shorter disease duration and higher CRP values, and the patients with high serum IL-13 levels did not respond to TCZ treatment [10]. SSc patients with high levels of serum IL-13 may be in the fibrotic stage and are considered to have lost reactivity to TCZ.

Another problem is how to evaluate the effect of anti-cytokine treatment. The historical judgement that mRSS must be used as the main evaluation criterion renders the development of therapeutic drugs for SSc treatment difficult. From the results of the focuSSced study, it is obvious that it is not appropriate to use mRSS as an evaluation method for large-scale studies. In large-scale clinical trials, the evaluated value should be closer to the true value; however, there will also be a greater variation in the mRSS. We used a Vesmeter [11] and several other devices have been proposed to evaluate the skin involvement of SSc including the Durometer [12] and Cutometer [13]. If the most appropriate target of anti-cytokine drugs is the skin, studies should use such a device. As a result, spirometry appears to be the most suitable evaluation method for TCZ. Because factors involved in the pathogenesis of SSc are considered to differ depending on the disease stage and affected organs, it is important to use an effective evaluation method.

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