ABSTRACT
Systemic sclerosis (SSc) is a multi-organ systemic disorder characterized by excessive collagen deposition. This disease is usually classified into two clinical subsets – diffuse cutaneous SSc (dSSc) and limited cutaneous SSc (lSSc). We have proposed low-dose oral corticosteroid treatment with indication criteria consisting of the following three conditions: (1) early onset; (2) edematous changes; and (3) rapid progression. Cases satisfying 2 or 3 criteria have a definite indication, while those meeting 0 or 1 criterion have no indication.

We treated 23 cases of dSSc by low-dose oral corticosteroid (prednisolone 20 mg/day as the initial dosage) and evaluated the effect using the modified Rodnan total skin thickness score (mRodnan TSS). The mean initial TSS (20.3 ± 9.3) decreased significantly to 12.8 ± 7.0 after one year of treatment (p < 0.005) and to 8.7 ± 6.1 at final evaluation (p < 0.001).

Thus, we confirmed the usefulness of oral corticosteroid treatment for early dSSc in Japanese patients.

Introduction
Systemic sclerosis (SSc) is a systemic disease characterized by fibrotic changes in many organs including the skin, lung, esophagus, and kidney (1). SSc is also characterized by autoimmunity demonstrating disease-specific auto-antibodies (2) and signs of vascular damage such as Raynaud’s phenomenon. Although there is no treatment that can cure SSc, both the morbidity and the mortality have improved significantly over the last two decades (3), probably because of a better understanding of the pathogenesis and treatment of the disease to keep it under control by general physicians.

Moreover, many disease-modifying drugs have been investigated in this decade by multi-center, randomized double-blind control studies, although no standard treatment has yet been established. As described previously, the presence of autoimmunity, early inflammatory cell infiltrations of the affected organs and elevated serum levels of cytokines derived from activated immune cells have led to trials of many immunosuppressive treatments.

The most classical and common immunosuppressive drugs are corticosteroids, although these agents have not been widely accepted for the treatment of SSc. Szczepanski described the prevailing opinion regarding this therapy in Jablonska’s well-known textbook as follows (4). “Follow-up of the patients, however, showed that the improvement is transient and that deterioration sets in after the treatment is discontinued. Prolonged steroid administration is hazardous because of the antianabolic effect. Depending on how long patients treated with corticosteroids were followed up, opinions as to their efficacy are divided. Some authors think that their effect is beneficial.” Moreover, Steen et al. reported that administration of more than 40 mg/day of prednisolone increased the risk of renal crisis (5).

However, in the past decade, we have experimented with low-dose corticosteroid therapy (starting with 20 mg/day and decreasing to 2.5-10 mg/day of prednisolone for maintenance), targeting early diffuse rapid progressive diffuse cutaneous SSc (dSSc). This was not a controlled study, although we have had successful results in many cases. Here we report a summary of this study.

Patients and methods
Patients
Twenty-three patients with early rapid progressive dSSc were treated by low-dose corticosteroid therapy between
There were 3 male patients and 20 female patients. These patients satisfied at least two of the treatment criteria for corticosteroid therapy described below.
1. Early dSSc (within two years after the onset of skin sclerosis).
2. Clinically edematous sclerotic stage.
3. Rapid progression (an increase of at least 4 or more on the modified Rodnan total skin thickness score (m Rodnan TSS) within 6 months).

Patients with the complications listed below were excluded.
1. Active myositis requiring more than 20 mg/day of prednisolone.
2. Active pulmonary disease requiring other immunosuppressive therapy such as cyclophosphamide pulse therapy or oral cyclosporine treatment.
3. Chronic infectious diseases.

**Treatment**
The initial dosage of prednisolone was 20 mg/day, which continued for 2-8 weeks. After improvement in the edematous and skin sclerosis signs, the dose of prednisolone was decreased by 2.5 mg/day every 2-6 months. The usual maintenance dosage was 2.5-10 mg/day.

**Evaluation**
The end-point of this trial was changes in the m Rodnan TSS observed by the same dermatologist. m Rodnan TSS was measured before treatment, after one year and at the final evaluation.

**Results**

**Changes in the m Rodnan TSS**
Table I shows that a significant decrease in TSS in all 23 patients was observed both after 1 year (20.3 ± 9.3 versus 12.8 ± 7.0, p < 0.005) and at the final evaluation (20.3 ± 9.3 versus 8.7 ± 6.1, p < 0.001).

Table II summarizes the findings on final evaluation of these patients; 69% were estimated to have good response (less than 50% final TSS). Only two patients did not respond to the therapy. Figure 1 shows 5 typical successful cases and Figure 2 shows 3 cases that were relatively resistant to this therapy.

**Side effects**
There was no renal crisis in any of these 23 patients. One patient developed carinii pneumonia which responded to antibiotic treatment.

**Discussion**
Here we report the successful treatment of skin sclerosis with low-dose corticosteroids in Japanese dSSc patients. We conclude that this treatment may be useful for carefully selected patients. However, several issues should be clarified:
1. The incidence of renal crisis in Japanese patients is very low at 2-3%, which is much lower than that reported in other countries. There may be a
lower risk of triggering renal crisis in Japanese patients.

2. Low-dose corticosteroid therapy is not effective for active lung disease, which requires more aggressive treatment such as cyclophosphamide pulse therapy.

3. There is no evidence-based controlled study data that low-dose corticosteroid treatment for early, diffuse, rapidly progressive SSc improves the prognosis, nor the QOL in these patients.

4. In SSc, various differences in the incidence of organ involvement and the frequency of disease-specific autoantibodies related to ethnic origin have been pointed out. The response to corticosteroids may also show a racial difference that is limited to Japanese patients. There are still many unsolved problems, but our therapy may be one of the treatment options if patients are carefully selected and followed.

Acknowledgement

I was the first Japanese researcher to work in Dr. LeRoy’s laboratory (1984-1987). Since then, more than 10 Japanese dermatologists have undergone training in his laboratory. In Japan, many dermatologists are working on scleroderma due to Dr. LeRoy’s excellent teaching system for Japanese investigators, and I greatly appreciate and acknowledge his world-wide leadership. In his memory I vow that my colleagues and I will do our best to contribute to reaching a better understanding of the pathogenesis of this disease and the finding of an effective therapy.

References

5. Steen VD, Medsger Jr TA: Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 41: 1613.