A randomised, double-blind, placebo-controlled trial: intravenous immunoglobulin treatment in patients with diffuse cutaneous systemic sclerosis

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Received on January 21, 2013; accepted in revised form on February 20, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 76): S151-S156.

Key words: systemic sclerosis, IVIG, DBT

Competing interests: K. Takehara is a clinical consultant of this trial; the other co-authors have declared no competing interests.

ABSTRACT

Objectives. *This paper aims to investigate the efficacy of intravenous immunoglobulin (IVIG) for skin sclerosis in diffuse cutaneous systemic sclerosis (dcSSc) by a randomised, double-blind, placebo-controlled, multicentre trial (DBT) with subsequent long-term observational and readministration studies.*

Methods. *In DBT, IVIG (400mg/kg/day for 5 consecutive days: a single course) or placebo (P) was intravenously administered to 63 dcSSc patients of 17 medical institutions in Japan, and changes in the modified Rodnan skin thickness score (MRSS) 12 weeks after administration or at discontinuation were compared as a primary endpoint. Patients with a 5-point or more improvement in the MRSS were continuously observed (long-term observational study), whereas IVIG was administered to those with less than a 5-point improvement (readministration study).*

Results. *In DBT, changes in the MRSS (mean±SD) were -3.3±4.2 and -4.2±4.6 in IVIG and P groups, respectively, and were not significantly different. Non-responder patients were subsequently subjected to the readministration study, and the change in the MRSS (LS-mean±SEM) at 60 weeks after the first administration was -8.3±1.0 in the IVIG → IVIG (GG) group treated with two courses of IVIG administration and -4.1±1.1 in the P → IVIG (PG) group treated with a single course of IVIG administration. The GG group represented a significant improvement in the MRSS against the PG group (p=0.0040).*

Conclusion. *Although the primary endpoint was not achieved in DBT, repeated administration of IVIG for two courses may be effective for skin sclerosis in dcSSc. Further investigation by the administration of plural courses will be necessary.*

Introduction

Systemic sclerosis (scleroderma or SSc) is a disease characterised by fibrosis of the skin and visceral organs, and extracellular matrix, mainly type I and type III collagen, is excessively deposited. The cause is unclear, but autoimmune phenomena, collagen metabolism, overproduction of growth factors and cytokines, vascular disorders, hereditary backgrounds, and environmental factors are considered to be entangled in a complex way to form the pathology. The disease is classified as an autoimmune disease because autoantibodies against cell nuclear components, such as topoisomerase I and centromere, are frequently detected (1, 2). In diffuse cutaneous SSc (dcSSc), skin sclerosis expands toward proximal regions of the elbow and knee and acutely aggravates, and pulmonary, renal, and myocardial impairments occur frequently.

Since fibrotic lesions in SSc are less reversible, the main objective of treatment is set at the prevention of organ disorders and inhibition of progression when impairments are already present. Many agents have been investigated as therapeutic drugs to inhibit the progression of SSc, although no drug has demonstrated clear efficacy for the improvement of skin sclerosis by a multicentre, randomised, double-blind, controlled study (3-7).

Intravenous immunoglobulin (IVIG) has been used as an important therapeutic drug for many clinical conditions, such as primary immunodeficiency and autoimmune diseases and acute inflammatory conditions, for a long time (8). IVIG acts based on the function of natural antibodies, a factor of homeostasis maintenance in healthy individuals (9). It is also assumed to exhibit an immunomodulatory action against incontinence of the immunoregulatory system

in various diseases and improve pathological conditions.

Levy *et al*. (10, 11) performed 3–6 courses of IVIG therapy in 5 limited cutaneous SSc (lcSSc) and 10 dcSSC patients, in whom a single course was comprised of IVIG administration at 400 mg/kg/day for 5 consecutive days monthly, and achieved improvements in the modified Rodnan skin thickness score (MRSS). Nacci *et al*. (12) administered IVIG at 2 g/kg per month for 6 months to 5 lcSSC and 2 dcSSC patients with severe joint involvement, and observed improvements in the MRSS, joint pain, tenderness, hand function, and quality of life (QOL). Ihn *et al*. (13) and Asano *et al*. (14) administered a single course of IVIG therapy comprised of IVIG administration at 400 mg/kg/day for 5 consecutive days to 5 dcSSc patients, and observed an effect from 2 weeks after the initiation of administration. They observed improvements in the MRSS in all patients at 12 weeks, and improvements continued thereafter in 4 patients.

Since the collagen-metabolising function could be destroyed by an immunological mechanism in the pathology of SSc, the normalisation of immune function is considered important, and IVIG treatment is expected to show efficacy for SSc. IVIG does not excessively inhibit immunity and is not categorised as immunosuppressors such as oral steroids and cyclosporine.

To evaluate the efficacy and safety of a single-course administration of IVIG for skin sclerosis in dcSSc, we performed the first randomised, double-blind, placebo-controlled, multicentre trial (DBT) in which we examined the effect of IVIG for dcSSc of 17 medical institutions in Japan and subsequent long-term observational and readministration studies.

Methods

The study protocols were approved by the Institutional Review Board of each participating institutions, and the trials were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice in 17 medical institutions in Japan. DBT was registered in ClinicalTrials.gov (number NCT 00348296).

Study design

The outline of the study design is shown in Figure 1. In DBT, to exclude subjects in whom the disease was improved by drugs administered before this study, the MRSS was determined at provisional registration, 6 weeks after provisional registration, and at definitive registration, and subjects with no change (within 2 points) or exacerbation (a 3-point or more increase) over the 12-week period from provisional registration were included in definitive registration. Subjects received an intravenous infusion of IVIG (Venoglobulin-IH®, Japan Blood Products Organisation, Tokyo, Japan) or indistinguishable placebo at 400mg (8 mL)/kg/day for 5 consecutive days (a single course). The corticosteroid (at a dose exceeding 15 mg/day as prednisolone) and disease-modifying drugs were not allowed throughout the clinical trial period.

To observe persistence of the effect, responder subjects in whom a 5-point or more improvement in the MRSS was noted 12 weeks after investigational drug administration were subjected to the long-term observational study to observe the condition, and subjects with less than a 5-point improvement in the MRSS were subjected to the readministration study in which IVIG (a single course) was administered. To assure the data in DBT, a 12-week data fixation period was set before IVIG readministration.

Patients

The conditions required for provisional registration were an age of 16 years or older at the time of obtaining informed consent and dcSSc with a 20-point or higher MRSS regardless of gender. Any of the following patients who did not respond to corticosteroids and/or other disease modifying drugs adequately could not be treated with corticosteroids and/or other disease modifying drugs due to complications, and lost the suitable treatment period with corticosteroids and/or other disease modifying drugs judging from the symptoms and history of the disease were selected.

Patients complicated by severe hepatic, renal, and cardiac disorders and malignant tumours, with a past medical history of cerebral infraction or its symptoms, and previously diagnosed with IgA deficiency were excluded on provisional registration.

Efficacy assessment

The primary endpoint in DBT was set at MRSS changes 12 weeks after administration or at discontinuation from that at definitive registration. The MRSS

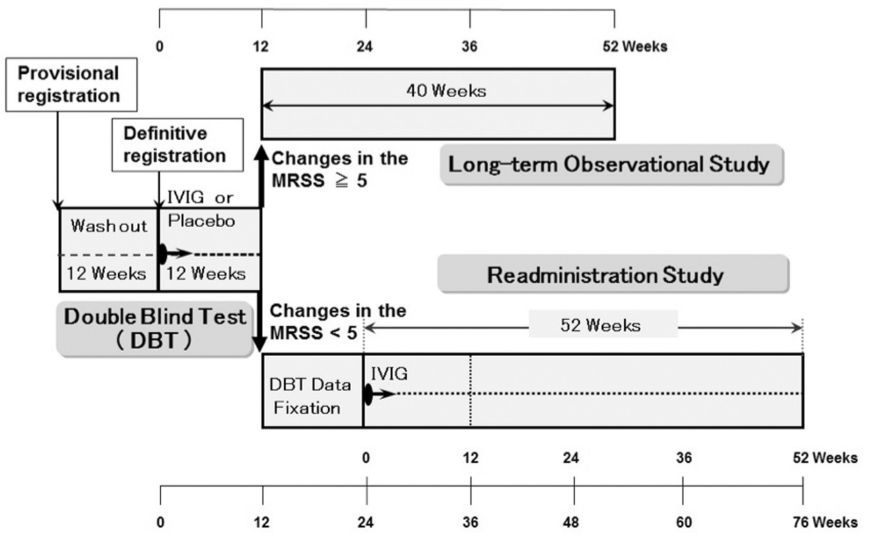

Fig. 1. Outline of the study design.
IVIG or placebo were administered to subjects after a definitive registration. MRSS changes 12 weeks after administration or at discontinuation from that at definitive registration were assessed. Subjects with a 5-point or more improvement in the MRSS were observed in the long-term observational study. IVIG was readministered to subjects with less than a 5-point improvement in the MRSS after DBT data fixation in the readministration study.

has been used as a standard evaluation item in SSc related clinical studies (3-7). To unify MRSS assessment criteria, raters were gathered and trained before study initiation. The number of MRSS raters was limited to two in each institution, and they rated the same patients as much as possible.

The following items were selected for the secondary endpoint of efficacy: dermal fibrotic thickness, joint range of motion (hand, elbow, and knee), oral aperture, hand extension, hand flexion, health assessment questionnaire, respiratory function (%VC, %DLco), and interstitial pneumonia. Skin samples biopsied from the extensor side of the forearm were blinded by a third party, and dermal thickness was measured by the same measurer.

Statistical analyses

Statistical analyses in DBT were independently performed, and those of the long-term observational and readministration studies were integrated with those in DBT. All statistical analyses were performed based on Intent-To-Treat, *i.e.* when baseline and subsequent at least one observation data were present, all data of the allocated patient were included in analysis.

DBT

For the bias of demographics or baseline between groups, measured values and rank data were analysed employing the matched paired ranked Wilcoxon test, and categorical data were analysed employing Fisher's exact test. Regarding the primary endpoint, MRSS changes 12 weeks after administration or at discontinuation from that at definitive registration were compared between groups using the Wilcoxon signed-rank test. In addition, changes in secondary endpoints after administration were similarly analysed.

Long-term observational and readministration studies

MRSS changes in DBT were integrated with results of the long-term observational or readministration study, and the repeated measurement analysis (covariance structure type: compound symmetry) combining between-group comparison, time-point, and interaction in the model was performed regarding the score before administration as a covariance and the comparison between the groups to used LSD (Least square difference) in each time-point. Results were presented as the LS-mean±SEM.

Table I. Baseline demographic data.

	IVIG n=31	Placebo n=31	*p*-value[a]
Female	24 (77.4)	24 (77.4)	1.0000
Age (year)	54.3 ± 12.1	53.8 ± 11.0	0.9775
Disease duration (year)	6.05 ± 7.41	5.76 ± 6.32	0.9888
MRSS	29.2 ± 6.0	27.8 ± 6.4	0.2676
History of corticosteroids at enrolment	23 (74.2)	24 (77.4)	1.0000
History of disease modifying drugs at screening	17 (54.8)	12 (38.7)	0.3087
Anti-topoisomerase I antibody	17 (54.8)	18 (58.1)	1.0000
Anti-U1-RNP antibody	2 (6.5)	4 (12.9)	0.6713
Anti-centromere antibody	5 (16.1)	4 (12.9)	1.0000

Values are mean±SD for continuous variables and n (%) for categorical variables.
[a]*p*-values for categorical variables were calculated with Fisher's exact tests, and *p*-values for continuous variables were calculated with *t*-tests.

Results

Patient population

In DBT, 71 patients signed informed consent, and 64 were registered and randomly allocated to IVIG or P groups. The investigational drug was administered to 63 subjects, and 59 subjects completed DBT and progressed to the next study (long-term observational study: 20, readministration study: 39). In the readministration study, 36 subjects were treated with IVIG.

DBT

i. Demographic characteristics

Table I shows patient backgrounds. No bias was noted in backgrounds between the groups (allocation factors: gender, with or without corticosteroid treatment, and the median MRSS on definitive registration).

ii. Primary endpoint

Figure 2 shows changes in the MRSS. MRSS changes (mean±SD) 12 weeks after administration or at discontinuation were -3.3±4.2 and -4.2±4.6 in IVIG and P groups, respectively, with no significant differences between the groups.

iii. Secondary endpoints

Percentage changes in dermal fibrotic thickness (mean±SD) were -2.23±34.48 (n=21) and 7.51±25.55 (n=22) in IVIG and placebo groups, respectively, showing that thickness decreased more in the IVIG group than that in the P group, but this decrease was not statistically significant. No significant difference was noted in any other secondary endpoint between the groups.

iv. Safety evaluation in DBT

Adverse drug reactions were noted in 32.3% (10/31) and 12.5% (4/32) of IVIG and P groups, respectively, and abnormal changes in laboratory test values were noted in 25.8% (8/31) and 12.5% (4/32), respectively. The main adverse drug reactions of IVIG were fever and elevations in CRP and ALT.

Long-term observational and readministration studies

i. Long-term observational study

The results of repeated measurement analysis of MRSS changes are shown in Figure 3. A significant difference was noted only in the evaluation week. The MRSS rapidly decreased from -4.9±1.2 (LS-mean±SEM) at one week after administration to -9.2±1.2 at 8 weeks, and this reduction was maintained at 52 weeks (-9.7±1.2) in the IVIG group. In the P group, although the reduction was slower than that in the IVIG group, the MRSS decreased from -3.9±1.0 at one week after administration to -7.6±1.0 at 8 weeks, and this reduction was maintained at 52 weeks (-11.7±1.1).

ii. Readministration study

The results of repeated measurement analysis of MRSS changes are shown

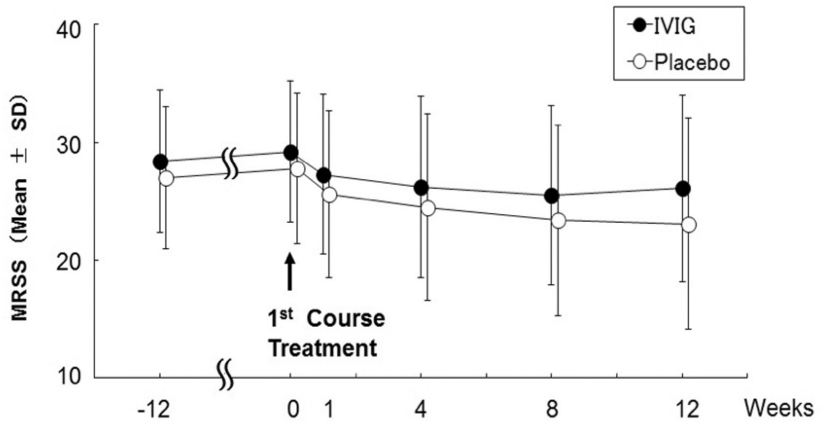

Fig. 2. Course of the MRSS in DBT.
Between IVIG and placebo groups, MRSS changes were not significantly different at any time during the 12-week trial.

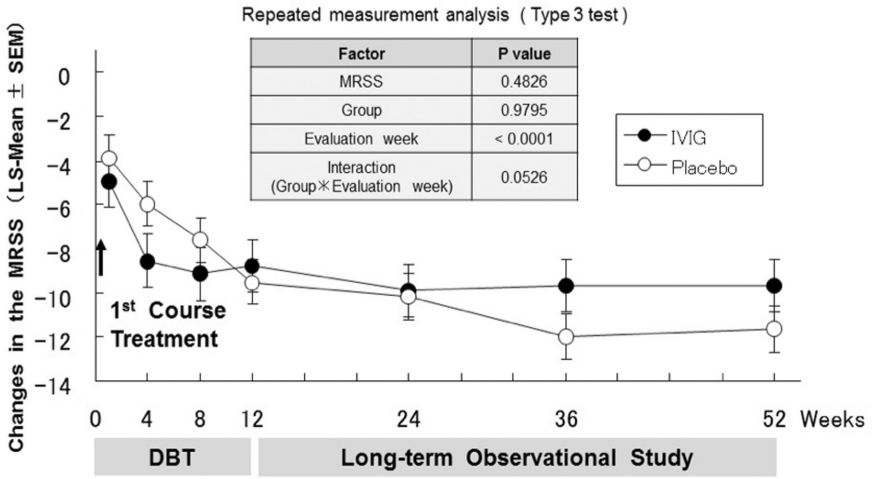

Fig. 3. Changes in the MRSS in the long-term observational study.
Subjects with a 5-point or more improvement in the MRSS in DBT were observed. The repeated measurement analysis combining between-group comparison, time-point, and interaction in the model was performed regarding the score before administration as a covariance and the comparison between the groups to used LSD in each time-point. No significant difference was noted in the MRSS change between the groups.

in Figure 4. Significant differences were noted in the evaluation week and interaction (group and evaluation week). Almost no change was noted in the MRSS in the first course in either group, but the second course of IVIG administration (24 weeks after the first administration) decreased the score from -1.4±1.0 (LS-mean±SEM) to -5.7±1.0 at 32 weeks, and the score continuously decreased until 60 weeks in the IVIG → IVIG (GG) group. In the P → IVIG (PG) group, the score decreased from -1.3±1.0 to -5.0±1.0 at 32 weeks, but no further decrease was noted. At 60 weeks, scores (LS-mean±SEM) were -8.3±1.0 and -4.1±1.1 in GG and PG groups, respectively, showing a significant decrease (LSD difference: p=0.0040; 95% confidence interval for the difference: -7.1 ~ -1.4), and this is the reason for the significant difference observed in interaction.

iii Safety evaluation in the readministration study

In the readministration study in which IVIG was administered, the incidences of adverse drug reactions were 38.9% (7/18) and 31.6% (6/19) in GG and PG groups, respectively. The incidences of abnormal changes in laboratory test values were 5.6% (1/18) and 15.8% (3/19), respectively, showing that the incidence was not markedly increased by the second course of treatment.

Discussion

No significant difference was noted in the primary endpoint, MRSS change, between IVIG and P groups, but significant improvements in the MRSS were noted in the GG group over those in the PG group in the readministration study, suggesting that the efficacy of a single course of administration is insufficient for patients with this disease requiring IVIG, but readministration (multiple courses) may decrease MRSS. In addition, dermal fibrotic thickness generally tended to improve in the IVIG group in DBT, and this tendency was marked in patients confirmed to be responders based on the MRSS at 12 weeks.

We expected IVIG to exhibit an effect after a single course similar to that for other autoimmune diseases, based on reports from Ihn *et al*. (13) and Asano *et al*. (14), but no efficacy was observed in this placebo-controlled study.

The pharmacological actions of IVIG on cells of patients with SSc and experimental SSc models have been reported. In a report in which IVIG was administered to tight skin mice twice a week for 4 weeks (total dose: 2 g/kg), collagen expression and type I collagen gene expression in skin tissue decreased, and TGF-β1 and IL-4 production by splenocytes significantly decreased, showing that IVIG improved these parameters involved in skin fibrosis (15). Skin fibrosis accompanied by skin collagen production was shown to be caused in a mouse model of skin fibrosis induced by subcutaneous administration of bleomycin (9), and it has been reported that IVIG inhibited collagen production by inhibiting macrophage accumulation in skin fibrotic lesions and MCP-1 and TGF-β production in macrophages and monocytes involved in the activation of fibroblasts (16). Furthermore, it has been confirmed by functional analysis of human skin fibroblasts that type I procollagen, TGF-β receptors, and α-SMA involved in fibrosis were more strongly expressed in skin fibroblasts of dcSSc patients than those in healthy subjects, whereas MMP-1, which destroys fibrotic regions, was not expressed; however,

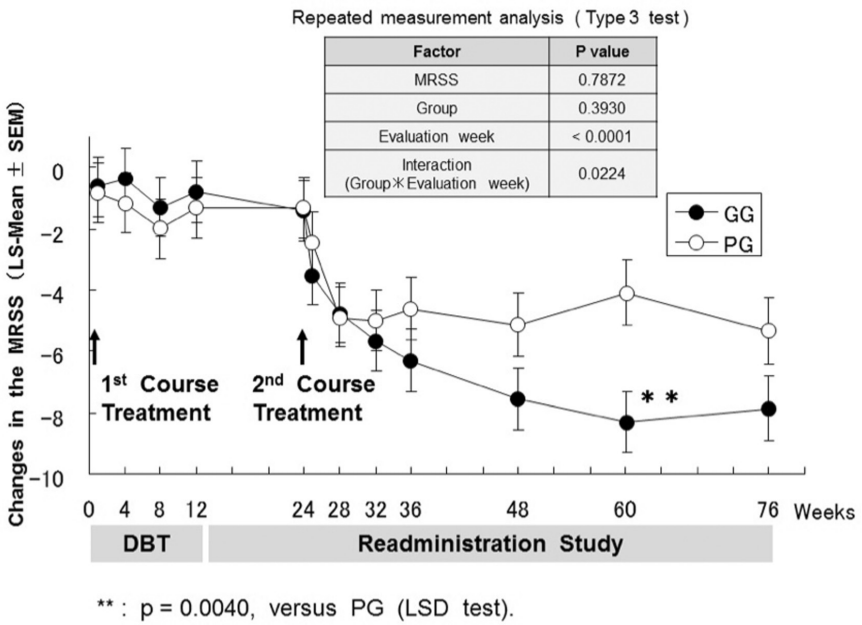

Fig. 4. Changes in the MRSS in the readministration study.
Subjects with less than a 5-point improvement in the MRSS in DBT were enforced in the 2nd course treatment. The repeated measurement analysis combining between-group comparison, time-point, and interaction in the model was performed regarding the score before administration as a covariance and the comparison between the groups to used LSD in each time-point.

the expressions of all factors were improved to normal levels 12 weeks after a single-course administration of IVIG (14).

Based on the above, it was suggested that IVIG inhibits fibrosis by acting on immune function. Although we did not have a chance to measure cytokines, it is assumed that IVIG exhibits its inhibitory effect at the cytokine level.

Only a few clinical studies on the efficacy of IVIG for skin sclerosis in dcSSc have been performed, and these were pilot studies. We performed first DBT and subsequent long-term studies of IVIG in dcSSc patients, which is very significant. Since the cause of dcSSc is complex and markedly heterogeneous, it may be difficult to demonstrate the efficacy of drugs by a comparative study. In other countries, multiple-course administration of IVIG for SSc, such as the administration of a single course/month for 6 months, was performed (10-12). Since two-course administration of IVIG exhibited an MRSS-improving effect in the readministration study, further investigation with multiple-course treatment including the timing of treatment is necessary to demonstrate the usefulness of IVIG.

Acknowledgements

The authors wish to thank the members of this study group. Primary investigators in the medical facilities who participated in this study; Hiroki Takahashi (Department of Sapporo Medical University School of Medicine); Osamu Ishikawa (Department of Dermatology, Gunma University Graduate School of Medicine); Takayuki Sumida (Division of Clinical Immunology, Graduate School of Comprehensive Human Science, University of Tsukuba); Atsushi Hatamochi (Department of Dermatology, Dokkyo University School of Medicine); Masako Hara (Institute of Rheumatology, Tokyo Women's Medical University); Toshiyuki Yamamoto (Department of Dermatology, Fukushima Medical University); Masataka Kuwana (Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine); Norihito Yazawa (Department of Dermatology, Graduate School of Medicine, University of Tokyo); Hirahito Endo (Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine); Yoshinao Muro (Division of Connective Tissue Disease & Autoimmunity, Department of Dermatology, Nagoya University Graduate School of Medicine); Takashi Usui (Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University); Akihide Ohta (Division of Rheumatology, Department of Internal Medicine, Saga University); Yuji Inoue (Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University); Akimichi Morita (Department of Geriatric and Environmental Dermatology, Nagoya City University, Graduate School of Medical Sciences). The measurer of dermal thickness of biopsied skin samples who participated in this study; Yoshinao Soma (Department of Dermatology, St. Marianna University School of Medicine).

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