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Low-dose intravenous immunoglobulin as an adjunctive therapy for systemic sclerosis: real-world evidence from a single center

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Abstract

Background

Intravenous immunoglobulin (IVIG) has shown potential benefits for systemic sclerosis (SSc), but its high cost and supply instability may restrict the use of the 2 g/kg monthly regimen most commonly used in previous studies. We therefore evaluated the potential benefits of low-dose IVIG as an adjunctive therapy in patients with SSc using real-world data.

Methods

A single-center retrospective observational study was conducted in adults with SSc treated with at least two cycles of IVIG between 2014 and 2025. Patients with SSc who had never received IVIG served as controls. Propensity score matching was performed at a 1:3 ratio using age, sex, SSc-specific antibody profile, and rituximab or cyclophosphamide treatment history. The primary outcome was the 6-month change in modified Rodnan skin score (mRSS). Clinical outcomes were also compared between the first and last IVIG cycles in the IVIG group.

Results

Among 20 patients treated with IVIG, 19 were matched with 44 controls. At 6 months, mRSS decreased by 5.5 ± 6.9 in the IVIG group and by 1.8 ± 7.3 in the control group; however, the between-group difference was not statistically significant after multivariable adjustment (adjusted β = 2.436, 95% CI − 1.428 to 6.300, p = 0.224). In the IVIG group, mRSS decreased from 17.6 ± 9.7 at the first IVIG cycle to 12.0 ± 8.9 at the last IVIG cycle (p = 0.002), and the median glucocorticoid dose decreased from 7.5 [5.0–10.0] to 5.0 [3.4–7.5] mg/day (p = 0.013). Gastrointestinal improvement was observed in 9 of 16 patients (56%) with gastrointestinal involvement.

Conclusions

Low-dose IVIG did not significantly improve mRSS compared with matched controls. In the within-group analysis, gastrointestinal improvement was observed in more than half of IVIG-treated patients with gastrointestinal involvement, and IVIG was generally well tolerated. These findings suggest that low-dose IVIG may have potential as an adjunctive treatment for gastrointestinal involvement in SSc

1.Introduction

Systemic sclerosis (SSc) is a heterogeneous autoimmune disease characterized by progressive skin fibrosis and multi-organ involvement. Intravenous immunoglobulin (IVIG) has been used as an adjunctive therapy in patients with refractory disease or specific organ involvement. Previous studies have

suggested the potential of IVIG as a therapeutic option not only for skin fibrosis but also for musculoskeletal or gastrointestinal involvement, as well as for reducing glucocorticoid doses[1–3]. Most previous studies have used an IVIG regimen of 2 g/kg administered once monthly[4]. The high cost of immunoglobulin therapy and the global shortage of immunoglobulin products provide important practical reasons for considering lower-dose regimens[5]. Korea is no exception, with the high cost of IVIG treatment and uncertainty in its supply remaining important concerns. Given these practical challenges in maintaining regular IVIG administration, this study aimed to evaluate the potential benefits of low-dose IVIG in patients with SSc using real-world data.

2.Methods

2.1 patient selection

We conducted a single-center (Soonchunhyang University Seoul Hospital) retrospective observational study of patients with SSc between 2014 and 2025. We included all patients with SSc over 18years of age treated with at least two cycles of IVIG therapy. Diagnosis was made according to the 2013 American College of Rheumatology/European League against Rheumatism classification criteria. Patients with SSc who received IVIG therapy for other indications were excluded from the study. A control group was established from the remaining pool of SSc patients who had never received IVIG therapy. This study was approved by the Institutional Review Board of Soonchunhyang University Seoul Hospital (IRB No. SCHUH 2026-02-001) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived by the Institutional Review Board due to the retrospective nature of the study.

2.2 Data collection

Data were retrospectively retrieved from medical records. Three rheumatologists involved in patient care performed the clinical assessments and reviewed the medical records and investigation findings. For the IVIG group, data regarding the main indication for IVIG therapy, treatment modalities, duration of treatment, occurrence of adverse events, and reasons for treatment discontinuation were collected. Clinical data were assessed at the initiation of the first IVIG cycle, 6 months after treatment initiation, and at the time of the last IVIG cycle. For the control group, clinical data were collected at the first visit and at the 6-month follow-up. Cutaneous involvement was assessed using the modified Rodnan skin score (mRSS). Muscular involvement was defined as reduced muscle strength accompanied by elevated muscle enzyme levels. For lung involvement, interstitial lung disease patterns were classified using high-resolution computed tomography (HRCT), and pulmonary hypertension was classified based on right heart catheterization. Pulmonary function was assessed using forced vital capacity (FVC) (% predicted), diffusing capacity for carbon monoxide (DLCO) (% predicted). For gastrointestinal tract (GI tract) involvement, patients were evaluated by a rheumatologist and a gastrointestinal motility specialist, and objective tests were performed according to the suspected manifestation. Gastrointestinal involvement was defined by objective test findings. The following objective tests were used for classification: (1)

Erosive esophagitis: :gastrofibroscopy (GFS) (2) Nonerosive reflux disease (NERD) : GFS and multichannel intraluminal impedance-pH (MII-pH) (3) Esophageal dysmotility: high-resolution impedance Manometry (HRiM) (4) Gastroparesis: gastric emptying scintigraphy and contrast-enhanced abdominopelvic computed tomography (APCT) (5) small intestinal or colonic pseudo-obstruction : APCT (6) SIBO: hydrogen breath test (HBT) (7) constipation: colonic transit study (8) fecal incontinence: defecography. When follow-up objective testing was performed, the same modality was used to assess changes.

2.3 IVIG treatment and outcome assessment

IVIG was administered as an adjunctive therapy in combination with background immunosuppressive therapy at the discretion of the treating physician. No patient received IVIG monotherapy. The interval between IVIG cycles was at least 4 weeks. The dosage, number of cycles, and treatment duration were determined according to the clinical condition of each patient. In the propensity score–matched analysis, the primary outcome was the change in mRSS from the index date to the 6-month follow-up. Changes in other clinical outcomes were assessed over the same period. The index date was defined as the initiation of the first IVIG cycle in the IVIG group and the first visit in the control group. In a separate within-group analysis of the IVIG group, clinical outcomes at the first IVIG cycle were compared with those at the last IVIG cycle. Gastrointestinal improvement was predefined as symptomatic improvement accompanied by either a ≥ 50% reduction in the dose of medications used for symptom control or objective evidence of improvement on follow-up testing.

2.4 Statistical analyses

Statistical analyses were performed using R version 4.6.0 (R core team, 2026). Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data and as median [interquartile range (IQR)] for non-normally distributed data. Categorical variables were expressed as numbers and percentages.

Propensity score matching (PSM) was performed at a 1:3 ratio between the IVIG treatment group and the control group. Propensity scores were estimated using a logistic regression model including the following covariates: age, sex, SSc-specific antibody profile, and history of rituximab or cyclophosphamide treatment. A history of rituximab or cyclophosphamide treatment was defined as either a prior history of treatment or initiation within 1 month after the index date. Matching was conducted using the nearest neighbor method with a caliper width of 0.2 standard deviations of the logit of the propensity score. After matching, the balance of covariates between the two groups was assessed using standardized mean differences (SMD), with an SMD < 0.2 considered to indicate an acceptable balance. Age was defined as the age at the time of IVIG initiation for the IVIG group, and the age at the first visit for the control group. For covariates that remained unbalanced after matching (SMD ≥ 0.2) additional adjustment was performed using multivariable regression models in the final analysis.

Between-group differences in 6-month changes in clinical outcomes were assessed using regression analyses. For within-group comparisons between the first and last IVIG cycles, paired t-tests were used

for normally distributed continuous variables, whereas Wilcoxon signed-rank tests were used for non-normally distributed variables. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

3.Results

3.1 Baseline characteristics of the study population

Among the 20 patients in the IVIG group, 19 were included in the propensity score–matched analysis and were matched with 44 of 118 patients in the control group. Baseline covariate balance improved after matching, particularly for sex and SSc-specific antibody profile, although residual imbalance remained in age, mRSS, and history of rituximab or cyclophosphamide treatment (Table 1). In the matched cohort, disease duration at the index date was longer in the IVIG group than in the control group (40.0 [6.5–55.0] vs. 1.0 [1.0–24.0] months). The proportions of patients with limited and diffuse cutaneous SSc were similar between the two groups (47% vs. 48% and 53% vs. 52%, respectively). Interstitial lung disease was common in both groups (74% vs. 66%), whereas gastrointestinal involvement was more frequent in the IVIG group than in the control group (79% vs. 43%). Regarding treatment history, mycophenolate mofetil and glucocorticoid use was more frequent in the IVIG group than in the control group.

Table 1
Baseline characteristics and covariate balance of the study population before and after propensity score matching Panel A. Baseline characteristics and covariate balance before and after propensity score matching

	Univariable Analysis				**Multivariable Analysis**			
	Univariable β	95% CI		*p*-value	Adjusted β	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
mRSS	2.857	-1.037	6.751	0.158	2.436	-1.428	6.300	0.224
GC	-1.402	-3.774	0.970	0.253	-1.796	-4.260	0.667	0.161
FVC	-7.770	-15.875	0.335	0.067	-8.034	-16.524	0.457	0.071
DLCO	-8.598	-17.041	-0.156	0.053	-9.365	-18.292	-0.437	0.048
ESR	-2.584	-18.858	13.689	0.757	1.858	-14.670	18.387	0.827
CRP	0.315	0.055	0.574	0.022	0.334	0.078	0.590	0.014
Hb	-0.201	-0.771	0.368	0.492	-0.127	-0.713	0.459	0.674
TP	-0.234	-0.562	0.095	0.171	-0.187	-0.525	0.151	0.285
CK	-113.037	-411.828	185.753	0.465	-118.068	-448.210	212.073	0.490

	Before matching			After matching		
	IVIG (n = 19)	Control (n = 118)	SMD	IVIG (n = 19)	Control (n = 44)	SMD
Sex, n(%)			0.417			0.044
Women	13 (68.42)	101 (85.59)		13 (68.42)	31 (70.45)	
Age, mean ± sd	54.42 ± 14.35	51.03 ± 12.37	0.253	54.42 ± 14.35	51.55 ± 11.85	0.218
mRSS, mean ± sd	17.37 ± 9.5	8.82 ± 8.69	0.939	17.37 ± 9.5	13.16 ± 9.34	0.447
[a]Antibody profile, n(%)			0.207			0.053
Positive	10 (52.63)	50 (42.37)		10 (52.63)	22 (50)	
Negative	9 (47.37)	68 (57.63)		9 (47.37)	22 (50)	
[b]RTX or CYC, n(%)			0.741			0.205
Positive	11 (57.89)	28 (23.73)		11 (57.89)	21 (47.73)	
Negative	8 (42.11)	90 (76.27)		8 (42.11)	23 (52.27)	
IVIG: intravenous immunoglobulin, SMD: standard mean difference, SD: standard deviation, mRSS: modified Rodnan Skin Score, RTX: rituximab, CYC: intravenous cyclophosphamide						
[a]Defined as positivity for at least one of the following antibodies: anti-centromere antibodies, anti-topoisomerase I antibodies, or anti-RNA polymerase III antibodies.						
[b]Defined as a history of treatment with rituximab or cyclophosphamide.						
Panel B. Clinical characteristics in the propensity score–matched cohort						

3.2 Clinical outcomes in the propensity score–matched cohort

During the 6-month follow-up, patients in the matched IVIG group received a median of 5.0 [3.5–6.0] IVIG cycles, including the first cycle at the index date. At the 6-month follow-up, mRSS decreased from 17.4 ± 9.5 to 11.8 ± 7.8 in the IVIG group and from 13.2 ± 9.3 to 11.4 ± 8.9 in the control group (Table 2). The mean change in mRSS was 5.5 ± 6.9 in the IVIG group and 1.8 ± 7.3 in the control group. However, the between-group difference in mRSS change was not statistically significant in either the univariable or multivariable analysis (adjusted β = 2.436, 95% CI − 1.428 to 6.300, p = 0.224). Glucocorticoid dose decreased from 6.2 (5.0–9.4) to 5.0 (4.1–7.5) mg/day in the IVIG group and from 7.5 (4.8–12.5) to 5.0 (2.5–7.5) mg/day in the control group, with no significant between-group difference (adjusted β =

−1.796, 95% CI − 4.260 to 0.667, p = 0.161). FVC and DLCO decreased numerically in both groups, although the magnitude of decline was smaller in the IVIG group. The between-group difference in FVC change did not reach statistical significance, whereas the adjusted difference in DLCO change was statistically significant (adjusted β = −9.365, 95% CI − 18.292 to − 0.437, p = 0.048). Among the laboratory parameters, CRP showed a significant between-group difference after multivariable adjustment (adjusted β = 0.334, 95% CI 0.078–0.590, p = 0.014), while no significant between-group differences were observed for ESR, hemoglobin, total protein, or CK.

Table 2

Six-month clinical outcomes and between-group differences in the propensity score–matched cohort

Panel A. Clinical outcomes at the index date and 6-month follow-up

	IVIG				Control			
	N	Index	6-month	Change*	N	Index	6-month	Change
mRSS	19	17.4 ± 9.5	11.8 ± 7.8	5.5 ± 6.9	44	13.2 ± 9.3	11.4 ± 8.9	1.8 ± 7.3
GC dose[a] (mg/day)	18	6.2 (5.0–9.4)	5.0 (4.1–7.5)	2.1 ± 4.4	44	7.5 (4.8–12.5)	5.0 (2.5–7.5)	3.5 ± 4.9
FVC (% predicted)	18	73.1 ± 13.7	69.9 ± 12.3	3.2 ± 10.5	44	78.9 ± 18.0	68.4 ± 18.5	10.5 ± 15.3
DLCO (% predicted)	18	52.2 ± 16.4	50.0 ± 14.3	2.2 ± 8.8	39	78.8 ± 18.6	67.0 ± 19.3	11.8 ± 14.9
ESR (mm/h)	19	55.9 ± 34.0	55.0 ± 36.5	0.9 ± 37.3	44	40.8 ± 26.8	35.9 ± 22.2	4.9 ± 24.6
CRP (mg/dL)	19	0.2 (0.0–0.5)	0.1 (0.0–0.1)	0.3 ± 0.7	44	0.1 (0.0–0.2)	0.1 (0.0–0.3)	0.0 ± 0.4
Hb (g/dL)	18	12.3 ± 1.8	12.6 ± 1.9	-0.3 ± 1.3	44	13.0 ± 1.3	13.1 ± 1.2	-0.0 ± 1.0
TP (g/dL)	18	7.1 ± 0.8	7.2 ± 0.7	-0.1 ± 0.7	44	7.2 ± 0.7	7.0 ± 0.8	0.2 ± 0.5
CK (U/L)	16	80.5 (54.8–117.5)	71.5 (56.2–98.0)	3.6 ± 44.1	30	73.0 (49.8–108.0)	78.0 (48.5–103.2)	100.3 ± 530.3

IVIG: intravenous immunoglobulin, mRSS: modified rodnan skin score, GC: glucocorticoid, FVC: forced vital capacity, DLCO: diffusing capacity of the lung for carbon monoxide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin, TP: serum total protein, CK: creatine kinase

*Change was calculated as the value at the index date minus the value at the 6-month follow-up

[a]Glucocorticoid dose was defined as the average daily prednisolone-equivalent dose during the one-month period following the time of measurement.

Panel B. Between-group differences in 6-month changes

mRSS: modified rodnan skin score, GC: glucocorticoid dose, FVC: forced vital capacity, DLCO: diffusing capacity of the lung for carbon monoxide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin, TP: serum total protein, CK: creatine kinase

3.3 Characteristics of the IVIG group

Fourteen of the 20 patients in the IVIG group (70%) were women, and the mean age at IVIG initiation was 51.5 ± 13.7 years (Table 3). The median disease duration was 42.0 [6.8–58.5] months. Eleven patients

(55%) had diffuse cutaneous SSc, while nine (45%) had limited cutaneous SSc. Gastrointestinal involvement and interstitial lung disease were the most common organ manifestations, observed in 80% and 75% of patients, respectively. Among the objectively confirmed gastrointestinal manifestations, erosive esophagitis (55%) and esophageal dysmotility (50%) were the most frequent. Regarding previous treatments, most patients had received glucocorticoids (95%), mycophenolate mofetil (75%), and cyclophosphamide (60%).

Table 3
baseline characteristics of the IVIG group

Sociodemographic	**N**	**Value**
Women (n,%)	14	70
Age (years, mean ± SD)	20	51.5 ± 13.7
[a]Disease duration at IVIG initiation (months, median [IQR])	20	42.0 (6.8–58.5)
SSc subtype		
limited (n,%)	9	45
diffuse (n,%)	11	55
History of organ involvements		
Raynaud phenomenon (n,%)	17	85
Digital ulcers (n,%)	6	30
Muscular (n,%)	3	15
Heart (n,%)	0	0
Scleroderma renal crisis (n,%)	0	0
Interstitial lung disease (n,%)	15	75
Pulmonary hypertension (n,%)	1	5
Gastrointestinal tract (n,%)	16	80
Erosive esophagitis (n,%)	11	55
Nonerosive reflux disease (n,%)	5	25
Esophageal dysmotility (n,%)	10	50
Gastroparesis (n,%)	2	10
IVIG: intravenous immunoglobulin, SD: standard deviation, SSc: systemic sclerosis, limited: limited cutaneous, diffuse: diffuse cutaneous, ANA: antinuclear antibodies, ACA: anti-centromere antibodies, Anti Scl-70: anti-topoisomerase I antibodies, Anti-RNA pol III: Anti-RNA polymerase III antibodies, Anti-SSA: Anti-SSA/Ro antibodies, RF: rheumatoid factor, Anti-CCP: Anti-Cyclic Citrullinated Peptide Antibodies, NFC: nailfold capillaroscopy		
[a]Since systemic sclerosis diagnosis		
[b] Acid suppressant: Histamine-2 receptor antagonists or Proton pump inhibitors or Potassium-competitive acid inhibitors		

Sociodemographic	N	Value
Chronic intestinal pseudo-obstruction (n,%)	3	15
Small intestinal bacterial overgrowth (n,%)	2	10
Constipation (n,%)	2	10
Fecal incontinence (n,%)	1	5
Gastric antral vascular ectasia (n,%)	1	5
Immunological profile		
ANA (n,%)	17	85
ACA (n,%)	4	20
Anti Scl-70 (n,%)	7	35
Anti-RNA pol III (n,%)	3	15
Anti-SSA (n,%)	4	20
RF (n,%)	3	15
Anti-CCP (n,%)	1	5
NFC : Scleroderma pattern (n,%)	19	95
History of treatments		
Methotrexate	4	20
Mycophenolate	15	75
Cyclophosphamide	12	60
Rituximab	4	20
Glucocorticoid	19	95
Endothelin receptor antagonists	5	25

IVIG: intravenous immunoglobulin, SD: standard deviation, SSc: systemic sclerosis, limited: limited cutaneous, diffuse: diffuse cutaneous, ANA: antinuclear antibodies, ACA: anti-centromere antibodies, Anti Scl-70: anti-topoisomerase I antibodies, Anti-RNA pol III: Anti-RNA polymerase III antibodies, Anti-SSA: Anti-SSA/Ro antibodies, RF: rheumatoid factor, Anti-CCP: Anti-Cyclic Citrullinated Peptide Antibodies, NFC: nailfold capillaroscopy

[a]Since systemic sclerosis diagnosis

[b] Acid suppressant: Histamine-2 receptor antagonists or Proton pump inhibitors or Potassium-competitive acid inhibitors

Sociodemographic	N	Value
Phosphodiesterase type 5 inhibitors	3	15
Acid suppressant[b]	18	90
Laxative	1	5
5-HT4 receptor agonists	8	40

IVIG: intravenous immunoglobulin, SD: standard deviation, SSc: systemic sclerosis, limited: limited cutaneous, diffuse: diffuse cutaneous, ANA: antinuclear antibodies, ACA: anti-centromere antibodies, Anti Scl-70: anti-topoisomerase I antibodies, Anti-RNA pol III: Anti-RNA polymerase III antibodies, Anti-SSA: Anti-SSA/Ro antibodies, RF: rheumatoid factor, Anti-CCP: Anti-Cyclic Citrullinated Peptide Antibodies, NFC: nailfold capillaroscopy

[a]Since systemic sclerosis diagnosis

[b] Acid suppressant: Histamine-2 receptor antagonists or Proton pump inhibitors or Potassium-competitive acid inhibitors

3.4 IVIG treatment modalities

Gastrointestinal involvement was the most common indication for IVIG therapy (55%), followed by cutaneous (30%) and muscular involvement (15%) (Table 4). Patients received a median of 11.0 [6.2–28.2] IVIG cycles over a median treatment duration of 10.6 [7.3–42.9] months. The most commonly used regimen was 1.0 g/kg/day for 1 day (75%), followed by 0.5 g/kg/day for 1 day (20%) and 0.5 g/kg/day for 3 days (5%). Regarding associated treatments, all patients received oral glucocorticoids, and mycophenolate mofetil was the most commonly used immunosuppressive agent (90%), followed by cyclophosphamide (25%) and rituximab (15%).

Table 4
IVIG treatment modalities

Organ involvement motivating IVIG prescription	**N**	**Value**
Cutaneous (n, %)	6	30
Gastrointestinal tract (n, %)	11	55
Muscular (n, %)	3	15
Modalities		
Duration		
Number of cycles (median [IQR])		11.0 (6.2–28.2)
Treatment duration (months, median [IQR])		10.6 (7.3–42.9)
Dosage		
0.5g/kg/day for 1day (n, %)	4	20
1.0g/kg/day for 1day (n, %)	15	75
0.5g/kg/day for 3days (n, %)	1	5
Associated treatments		
Oral glucocorticoid (n, %)	20	100
Cyclophosphamide (n, %)	5	25
Rituximab (n, %)	3	15
Methotrexate (n, %)	1	5
Mycophenolate mofetil (n, %)	18	90
Tacrolimus (n, %)	1	5
Azathioprine (n, %)	2	10
IVIG: intravenous immunoglobulins, IV: intravenous		

3.5 Effectiveness of IVIG therapy

In the IVIG group, mRSS decreased from 17.6 ± 9.7 at the first IVIG cycle to 12.0 ± 8.9 at the last IVIG cycle (p = 0.002) (Table 5). The median glucocorticoid dose also decreased from 7.5 [5.0–10.0] to 5.0 [3.4–7.5] mg/day (p = 0.013). FVC decreased from 73.5 ± 14.1% predicted to 66.5 ± 11.9% predicted (p = 0.001). Gastrointestinal improvement was observed in 9 of 16 patients (56%) with gastrointestinal involvement. No significant changes were observed in ESR, CRP, hemoglobin, total protein, or CK.

Table 5
Characteristics of the IVIG group at first and at last IVIG cycles.

mRSS	N	First IVIG Value	Last IVIG Value	Change	*p*
	18	**17.6 ± 9.7**	**12.0 ± 8.9**	**5.611 ± 6.56**	**0.002**
GC dose[a] (mg/day)	20	7.5 (5.0–10.0)	5.0 (3.4–7.5)	2.5 (0–5)	0.013
FVC (% predicted)	17	73.5 ± 14.1	66.5 ± 11.9	7 ± 7.4	0.001
DLCO (% predicted)	18	52.6 ± 16.2	48.7 ± 12.9	3.833 ± 8.8	0.082
ESR (mm/h)	20	55.3 ± 33.3	54.5 ± 36.1	0.75 ± 29.57	0.911
CRP (mg/dL)	20	0.2 (0.0–0.5)	0.1 (0.0–0.8)	-0.01 (-0.14–0.15)	0.952
Hb (g/dL)	20	12.1 ± 1.9	12.1 ± 2.1	0.06 ± 1.3	0.839
TP (g/dL)	20	7.0 ± 0.8	7.1 ± 0.6	-0.02 ± 0.73	0.904
CK (U/L)	14	92.5 (61.2–177.5)	87.5 (48.5–135.8)	8 (-12.5–47.25)	0.530
GI improvement†, n/N (%)			9/16 (56%)		

IVIG: intravenous immunoglobulin, mRSS: modified rodnan skin score, GC: glucocorticoid, FVC: forced vital capacity, DLCO: diffusing capacity of the lung for carbon monoxide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin, TP: serum total protein, CK: creatine kinase, GI: gastrointestinal tract

[a]Glucocorticoid dose was defined as the average daily prednisolone-equivalent dose during the one-month period following the time of measurement.

†GI improvement was defined as either a reduction of ≥ 50% in the dose of medications used for symptom control or objective evidence of improvement on follow-up evaluation.

3.6 Safety of IVIG therapy

Two adverse events were noted during IVIG therapy: urticaria in one patient and nausea in another. Neither required hospitalization. IVIG was discontinued in 11 patients. The reasons for discontinuation were treatment success in two patients (improvement of cutaneous involvement in one and resolution of GAVE in the other), adverse events in two, treatment cost in six, and one unknown cause (out-of-hospital death)

4.Discussion

The proportions of patients with diffuse and limited cutaneous SSc were similar in our cohort. Among SSc-specific antibodies, anti-Scl-70 antibody was the most common in both the IVIG and control groups. Gastrointestinal and pulmonary involvement were the most frequent organ manifestations. Compared

with previous studies, one notable difference in the characteristics of our cohort was the relatively low prevalence of muscular involvement. The most distinctive difference in IVIG treatment modalities was the administered dose. Unlike the 2 g/kg regimen most commonly used in previous studies, the predominant regimens in our study were 1.0 g/kg/day for 1 day and 0.5 g/kg/day for 1 day[2–4].

Compared with the control group, low-dose IVIG did not result in a significantly greater reduction in mRSS. One possible explanation is that the IVIG dose used in our study may have been insufficient to produce an additional effect on cutaneous involvement, although this cannot be determined from the present study. Although the proportions of patients with diffuse and limited cutaneous SSc were similar between the groups, residual imbalance in baseline mRSS remained after propensity score matching and may have influenced the observed treatment effect. Therefore, our findings do not support a clear additional benefit of low-dose IVIG for cutaneous involvement beyond adjunctive therapy.

Low-dose IVIG was not associated with improvement in pulmonary function in either the comparison with the control group or the within-group analysis. Although the adjusted between-group difference in DLCO change reached statistical significance, pulmonary function declined numerically in both groups. Overall, these findings are consistent with previous studies in which IVIG did not demonstrate a clear beneficial effect on pulmonary function[2,3].

Regarding gastrointestinal involvement, previous observational studies have reported symptomatic improvement based primarily on questionnaire assessments [1–3]. In this study, which used lower-dose IVIG regimens, we aimed to assess gastrointestinal improvement using more objective criteria than symptom reporting alone. These criteria incorporated symptomatic improvement together with either a ≥ 50% reduction in the dose of medications used for symptom control or objective evidence of improvement on follow-up testing. Using these criteria, gastrointestinal improvement was observed in 56% of IVIG-treated patients with gastrointestinal involvement.

We recognize the substantial difference in disease duration between the IVIG and control groups, which may in part be related to the use of the first visit as the index date for the control group. As a tertiary referral center, we frequently encountered incomplete documentation regarding the onset or diagnosis of SSc in patients referred from other institutions. When reliable prior medical records were available, the documented onset or diagnosis was used to determine disease duration; otherwise, disease duration was calculated from the time of definitive SSc diagnosis at our institution. This may reflect, at least in part, the rarity of SSc and the fact that early clinical features associated with progression to definite SSc, as highlighted by the VEDOSS study, may not always have been recognized or documented before referral[6]. This approach may have contributed to the apparent difference in disease duration between the groups. In addition, because this study aimed to characterize gastrointestinal involvement in greater detail, using the first visit as the index date provided an opportunity to perform relevant investigations even in patients with relatively subtle gastrointestinal manifestations.

IVIG showed a good safety profile in our cohort. Only two adverse events were observed, and neither required hospitalization. This finding is consistent with previous studies of IVIG in SSc and other autoimmune diseases.[1,3,7]. Despite these potential advantages of IVIG, its high cost and supply instability remain important barriers to broader use. In our study, treatment cost was the most common reason for IVIG discontinuation. These practical limitations underscore the need to further investigate whether lower-dose IVIG regimens may provide a feasible treatment option for patients with SSc.

5.Conclusion

In conclusion, low-dose IVIG did not result in a significantly greater reduction in mRSS compared with matched controls. Gastrointestinal improvement was observed in more than half of IVIG-treated patients with gastrointestinal involvement, and IVIG was generally well tolerated. These findings suggest that low-dose IVIG may have potential as an adjunctive treatment option for gastrointestinal involvement in SSc, while its benefit for cutaneous involvement was not clearly demonstrated at the doses used in this study. Randomized clinical trials are needed to further define the role of low-dose IVIG in the treatment of SSc manifestations.

Declarations

Conflict of Interest

The authors disclose no conflicts.

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Author Contribution

SH. B. contributed to data curation, formal analysis, validation, and writing – original draft. KA. L. contributed to data curation, formal analysis, validation, visualization, and writing – review & editing. YS. H. contributed to data curation, formal analysis, and validation. HS. K. contributed to conceptualization, methodology, resources, investigation, supervision, project administration, and funding acquisition. All authors reviewed and approved the final manuscript.

Credit Authorship Contributions

Seong-Hyeok Bak: Data curation, formal analysis, writing - original draft, Validation, Kyung-Ann Lee: Data curation, Formal analysis, Validation, Writing - review & editing, Visualization, Yeon sik Hong: Data

curation, Formal analysis, Validation , Hyun-Sook Kim: Conceptualization, Methodology, Resources, Investigation, Supervision, Project administration, funding acquisition

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