Intravenous Immunoglobulin May Be an Effective Therapy for Refractory, Active Diffuse Cutaneous Systemic Sclerosis

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ABSTRACT. ***Objective.*** We sought to retrospectively review a single-center experience using intravenous immunoglobulin (IVIG) for the treatment of refractory, active diffuse cutaneous systemic sclerosis (dcSSc).

Methods. The mean modified Rodnan Skin score (mRSS) at baseline was compared to the mRSS at 6, 12, 18, and 24 months post-IVIG initiation by the paired Student t test. Changes in mRSS at 6 and 12 months were also compared to data from historical controls of 3 large, negative, multicenter, randomized clinical trials of other medications [D-penicillamine (D-pen), recombinant human relaxin (relaxin), and oral bovine type I collagen (collagen)] and to patients treated with mycophenolate mofetil (MMF) alone using the Student t test.

Results. Thirty patients were treated with adjunctive IVIG (2 g/kg/mo) for refractory, active dcSSc. The mean baseline mRSS of our cohort was 29.6 ± 7.2, and this significantly decreased to 24.1 ± 9.6 (n = 29, p = 0.0011) at 6 months, 22.5 ± 10.0 (n = 25, p = 0.0001) at 12 months, 20.6 ± 11.8 (n = 23, p = 0.0001) at 18 months, and 15.3 ± 6.4 (n = 15, p < 0.0001) at 24 months. The mean change in mRSS at 6 months was not significantly different in the IVIG group (–5.3 ± 7.9) compared to the relaxin trial (–4.8 ± 6.99, p = 0.74) or MMF group (–3.4 ± 7.4, p = 0.26); however, at 12 months, the mean change in mRSS was significantly better in the IVIG group (–8 ± 8.3) than in the D-pen (–2.47 ± 8.6, p = 0.005) and collagen (–3.4 ± 7.12, p = 0.005) groups, and was comparable to the group of primary MMF responders (–7.1 ± 9, p = 0.67).

Conclusion. Our observational study suggests that IVIG may be an effective adjunctive therapy for active dcSSc in patients failing other therapies. (First Release Dec 1 2014; J Rheumatol 2015; 42:236–42; doi:10.3899/jrheum.140833)

Key Indexing Terms:
DIFFUSE SCLERODERMA INTRAVENOUS IMMUNOGLOBULINS SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc, scleroderma) is a rare autoimmune disease characterized pathologically by fibrosis of the skin and internal organs, and a widespread arterial vasculopathy. Patients with active diffuse cutaneous disease often develop significant disability attributable to progressive skin thickening, intense discomfort from pruritus, burning in the skin, limitation in joint range of motion because of deep tissue fibrosis causing tendon friction rubs (TFR), and the development of contractures. To date, there is no proven therapy that consistently and effectively treats active cutaneous disease, although several immunosuppressive agents are thought to have some positive effects[1].

While intravenous immunoglobulin therapy (IVIG) is commonly used to treat other autoimmune diseases[2], its effects on patients with SSc remain unclear. In our SSc center, we have treated patients with IVIG if they have persistently active diffuse cutaneous disease that is refractory to other immunosuppressive agents. In our study, our primary objective was to retrospectively review our experience using IVIG for the treatment of active diffuse cutaneous SSc (dcSSc). We also examined changes in pulmonary function, organ involvement, and disability in patients treated with IVIG.

MATERIALS AND METHODS

Subjects were identified from the Johns Hopkins Scleroderma Center database, which has prospectively collected clinical information on consenting patients with SSc at 6-month intervals since 2000. All subjects included in our study had consented to participate. Our study database was approved by the Institutional Review Board. Clinical and laboratory data

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from patients previously treated with IVIG were reviewed. Patients who were treated with IVIG for active dcSSc, with or without another treatment indication such as myositis, were included in our study if longitudinal skin score data at prespecified intervals and IVIG initiation dates were available. Presence of active cutaneous disease was determined by the treating physician's clinical judgment. Our physician assessment of activity was based on a composite of the following clinical features: skin thickening as assessed by the modified Rodnan Skin score (mRSS), edematous skin changes, patient complaints of continued pruritus or discomfort of the skin, worsening flexibility, or active TFR. Patients without active cutaneous disease who received IVIG for the sole purpose of treating myositis or other indications were excluded. Our standard regimen for IVIG was 6 monthly cycles dosed at 2 g/kg/mo. Each cycle was administered over a course of 3 to 5 days, depending on the patient's tolerability. To be included, patients must have completed at least 3 cycles of IVIG infusions within the first 6 months of planned treatment. If a patient had multiple rounds of treatment, with at least a 3-month cessation of treatment between rounds, the first set of treatments was used for analysis.

Detailed clinical information, including data on age, sex, race, disease duration, concomitant and prior immunosuppressive medication use, pulmonary function test and echocardiography variables, disease severity scores, autoantibody status, and functional status [e.g., Health Assessment Questionnaire (HAQ)], were obtained from the clinical research database and medical records review. Patients were classified as having diffuse cutaneous disease if skin thickening was present on the trunk, abdomen, or proximal to the elbows and knees[3]. Treatment adverse effects were obtained from careful chart review. Reasons for discontinuing IVIG, either based on the physician's judgment of disease activity or adverse effects, were recorded.

Our primary outcomes of interest were the changes in the mRSS at 6 and 12 months compared to baseline, patient perception of disease activity as assessed by the HAQ, physician assessment, and improvement in TFR. Skin scores were obtained from the clinical research database, and all interval data points not identified in the database were abstracted from medical records where complete skin score data were recorded. Baseline mRSS were defined as the most recent score obtained during or up to 3 months prior to the month of initial IVIG treatment. Scores at the 6-, 12-, 18-, and 24-month windows were determined by time elapsed from the month of initial IVIG treatment and were restricted to ± 2 months of the target month. If the mRSS data were not available within this window, this timepoint was considered to have missing data. The patients assessed the disease activity using the HAQ-Disability Index (HAQ-DI) and a visual analog scale on the HAQ in response to the following question: "Overall, considering pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease today?" The physician's assessment of improvement or stabilization was based on the trajectory of the mRSS, TFR, flexibility, and cutaneous pruritus or discomfort as recorded in our database and patient visit notes. We also examined whether TFR resolved among patients who had TFR at baseline.

Data from historical controls were obtained from the pooled analysis of 3 large, negative, randomized clinical trials of D-penicillamine (D-pen), recombinant human relaxin (relaxin), and oral bovine type I collagen (collagen)[4]. Because of the negative outcome of these trials, we considered these data to be a close representation of the natural history of disease in patients with SSc. In addition, the IVIG cohort was compared to patients from our center treated with mycophenolate mofetil (MMF) alone[5]. Because the primary data were available from the MMF study[5], we were able to compare our IVIG cohort to a group of patients treated with MMF alone, who were typically deemed clinical responders. When interpreting these results, it was important to note that a large proportion of patients in the IVIG cohort were undergoing combination therapy with MMF and IVIG if the patients did not have a strong clinical response to MMF alone. Therefore, this analysis, in part, compared a group of MMF nonresponders (the IVIG cohort) to a group of MMF responders (MMF alone group). The mean change in mRSS at 6 months was available for the relaxin and MMF groups, and the mean change in mRSS at 12 months was available for the D-pen, collagen, and MMF groups. These data were compared to that of the IVIG cohort as detailed below.

Statistical analysis. Baseline mRSS of the IVIG cohort was compared to the mRSS at 6, 12, 18, and 24 months by the paired Student t test. Based on previously published data, we defined a decrease in mRSS of at least 5 points to be a minimal clinically important difference and indicative of a positive response to IVIG treatment[6]. We examined whether baseline clinical characteristics were predictive of this "cutaneous responder" status at 6 and 12 months by simple logistic regression analysis. Potential predictors of cutaneous response that were examined include age at SSc onset, race, sex, disease duration at IVIG initiation, number of IVIG treatments, IVIG treatment duration, reasons for discontinuing IVIG, concomitant immunosuppressive therapies, and autoantibody status (topoisomerase I and RNA polymerase III). We also examined whether these factors were predictive of the mean difference in mRSS at 6 and 12 months by simple linear regression analysis.

We further examined whether forced vital capacity (FVC), DLCO, disability (HAQ-DI and the HAQ patient self-assessment of disease activity), and organ involvement (defined by modified Medsger severity scales[7]) differed between baseline and at 12 months by the paired Student t test for continuous variables and by the Wilcoxon signed-rank test for ordinal variables. Descriptive data were also tabulated to detail improvements in creatinine kinase (CK) in patients who also had active myositis.

We compared the baseline characteristics of each negative clinical trial and of the MMF group to the IVIG cohort by the Student t test. The change in mRSS at 6 months was compared between the IVIG cohort and the relaxin and MMF groups using a Student t test. Similar comparisons at the 12-month timepoint were performed comparing the IVIG cohort to the D-pen, collagen, and MMF groups.

Additional sensitivity analyses that restrict data point windows to tighter time frames are detailed in Appendices 1 and 2. All statistical analyses were performed using Stata version 13.0 (Stata), and p values < 0.05 were considered statistically significant.

RESULTS

Thirty patients were treated for active diffuse cutaneous disease between 2004 and 2012 and met our inclusion criteria (Table 1). Of these, 24 (80%) were women and 26 (86.7%) were white. The mean age at IVIG initiation was 46.6 years (SD 12.3), and the mean disease duration at IVIG initiation was 24.6 months (SD 19.9). The mean baseline mRSS was 29.6 (SD 7.2). Five patients (16.7%) had concomitant myositis. The majority of patients (90%) had attempted other immunomodulatory or anti-fibrotic therapies without significant benefit based on the treating physician's clinical judgment (Table 1, Figure 1). Three patients initiated therapy with IVIG as part of first-line therapy: (1) 1 individual was treated with IVIG monotherapy in light of a recent malignancy and concern about risk of cancer recurrence with traditional immunosuppressive strategies; (2) another patient initiated IVIG treatment in combination with cyclophosphamide after only a short course of MMF (2 weeks of 3 g daily) because of rapidly progressive skin disease; and (3) 1 patient initiated concomitant MMF and IVIG in the context of a myositis overlap.

Patients received IVIG as part of routine clinical care, dosed at 2 g/kg/mo (Table 2). A typical round of treatment

Table 1. Baseline characteristics of IVIG cohort with comparison to the relaxin, D-Pen, collagen, and MMF studies.

Variable	IVIG, n = 30	Relaxin, n = 231	D-Pen, n = 134	Collagen, n = 168	MMF, n = 87
Age at drug initiation, yrs, mean (SD)	46.6 (12.3)	47.3 (10.3)	43.7 (12.4)	50.8 (12.2)	49.6 (11.2)
Duration from first non-Raynaud SSc symptom to drug initiation, mos, mean (SD)	24.6 (19.9)	26.4 (16.4)	9.5 (4.1)*	41.8 (31.9)*	24.4 (30.5)
Female sex, %	80.0	85.2	77.6	79.2	83.9
Race, %					
White	86.7	74.0	67.9*	76.2	78.0
Black	3.3	13.3	19.4*	16.1	17.1
Other	10.0	12.8	12.7	7.7	4.9
mRSS, mean (SD)	29.6 (7.2)	27.3 (6.9)	21.0* (8.0)	26.1* (7.8)	24.5 (9.5)*
HAQ-DI, mean (SD), n = 28	1.29 (0.70)				1.09 (0.65)
Concomitant myositis, n (%)	5 (16.7)				2 (2.3)*
TFR, n (%)	10 (33.3)				
Baseline CPK, mean (SD), n = 18	265.8 (440.6)				
Renal crisis, n (%)	0 (0)				
Pulmonary function, % predicted, mean (SD)					
FVC, n = 29	83.1 (19.2)				
DLCO, n = 28	76.8 (20.2)				
RVSP, mmHg, mean (SD), n = 19	32.1 (6.5)				
Medications used prior to IVIG initiation, n (%)					
Prednisone	19 (63.3)				
Methotrexate	8 (26.7)				
Azathioprine	3 (10.0)				
Cyclophosphamide	8 (26.7)				
D-Pen	3 (10.0)				
Hydroxychloroquine	8 (26.7)				
Minocycline	1 (3.3)				
Colchicine	1 (3.3)				
TNF inhibitor	2 (6.7)				
MMF	25 (83.3)				
Leflunomide	1 (3.3)				
Imatinib	2 (6.67)				
Rapamycin	1 (3.3)				
Other**	4 (13.3)				
Autoantibody status, n (%)					
ANA	29 (96.7)				
Anticentromere	0 (0)				
Antitopoisomerase 1 (Scl70)	5 (16.7)				
Anti-RNA polymerase III, n = 23	14 (60.9)				
RNP, n = 29	2 (6.9)				

* $p < 0.05$ for comparison with IVIG cohort. ** One patient was treated with gold for RA, 1 patient was treated with alefacept in a clinical trial, and 2 patients were treated with chemotherapeutic agents (cetuximab and docetaxel, respectively). IVIG: intravenous immunoglobulin; D-Pen: D-penicillamine; collagen: oral bovine type I collagen; MMF: mycophenolate mofetil; mRSS: Modified Rodnan Skin score; HAQ-DI: Health Assessment Questionnaire–Disability Index; TFR: tendon friction rubs; CPK: creatine phosphokinase; FVC: forced vital capacity; RVSP: right ventricular systolic pressure; TNF: tumor necrosis factor; ANA: antinuclear antibody, RA: rheumatoid arthritis; SSc: systemic sclerosis.

consisted of 6 monthly cycles of therapy. On average, patients completed 8.5 cycles of IVIG therapy (SD 5.3, range 3–24). Concomitant immunomodulatory or anti-fibrotic therapies included MMF (70%), prednisone (33.3%), cyclophosphamide (20%), methotrexate (10%), imatinib (3.3%), and hydroxychloroquine (3.3%).

Examination of changes in cutaneous disease activity and predictors of clinical response in the IVIG cohort. The mean mRSS progressively decreased from a baseline score of 29.6 (SD 7.2) to 24.1 (SD 9.6, n = 29, p = 0.0011) at 6 months, 22.5 (SD 10.0, n = 25, p = 0.0001) at 12 months, 20.6 (SD 11.8, n = 23, p = 0.0001) at 18 months, and 15.3 (SD 6.4, n = 15, p < 0.0001) at 24 months (Figure 1). Comparison of mRSS values at baseline and at 6 and 12 months showed

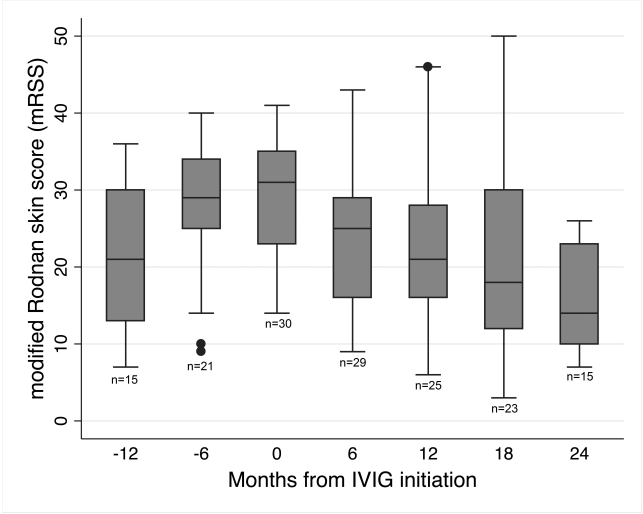

Figure 1. Trend in mean mRSS over time before and after IVIG initiation. mRSS: modified Rodnan Skin score; IVIG: intravenous immunoglobulin.

that 16 of 29 patients with available data were cutaneous responders (i.e., mRSS declined by at least 5 points) at 6 months, and 15 of 25 patients with available data were cutaneous responders at 12 months. We also examined whether these factors were associated with cutaneous responder status: age at SSc onset, race, sex, disease duration, number of IVIG treatments, IVIG treatment duration, reasons for stopping IVIG, concomitant immunosuppressive therapies, and autoantibody status. Concomitant prednisone use had a borderline negative association with cutaneous responder status at 12 months (OR 0.17, 95% CI 0.028–0.997, p = 0.05) but not at 6 months. Simple logistic regression analysis demonstrated that none of the other variables examined were predictors of cutaneous responder status at either timepoint. Changes in mRSS at 6 and 12 months were also examined as continuous variables, and there were no associations found with any of the examined covariates.

Disability, as assessed by the HAQ-DI, decreased, but the change was not statistically significantly different between baseline (mean 1.29, SD 0.70) and month 12 (mean 1.21, SD 0.75, p = 0.436). However, patients' self-assessment of disease activity improved significantly from baseline (mean 1.63, SD 0.72) to 12 months (mean 1.07, SD 0.76, p = 0.001). Based on the treating physician's assessment of disease activity, 60% of patients had clinically improved and 13.3% had stabilized. Ten patients in our cohort had TFR before initiating IVIG. Six months after initiating IVIG, 7 of these patients had resolution of TFR, 2 patients continued to have TFR, and in 1 patient, followup data at 6 months were not available.

Examination of changes in pulmonary function and organ involvement in the IVIG cohort. Pulmonary function remained stable from baseline to 12 months. The mean FVC at baseline and 12 months were 83.0% predicted (SD 19.6) and 83.8% predicted (SD 16.8, n = 28, p = 0.678), respectively. The mean DLCO at baseline and 12 months were 76.3% predicted (SD 21.0) and 79.9% predicted (SD 23.1, n = 25, p = 0.331), respectively. There were no statistically significant differences in Raynaud (p = 0.527), general (p = 0.711), cardiac (p = 1.0), pulmonary (p = 0.905), or gastrointestinal (p = 0.182) severity scores from baseline to 12 months. Renal severity scores remained unchanged for all

Table 2. Treatment details.

Variable	n = 30
Mean treatment length, mos, mean (SD)	9.4 (6.9)
Total number of IVIG cycles, mean (SD)	8.5 (5.3)
Concomitant medications*, n (%)	
Prednisone	10 (33.3)
Methotrexate	3 (10.0)
Cyclophosphamide	6 (20.0)
Hydroxychloroquine	1 (3.3)
Mycophenolate mofetil	21 (70.0)
Imatinib	1 (3.3)
Side effects, n (%)	
Headache, 1 with aseptic meningitis	12 (40.0)
Fatigue	7 (23.3)
Nausea and/or emesis	4 (13.3)
Fever	3 (10.0)
Arthralgias and/or myalgias	3 (10.0)
Rash and/or pruritis	3 (10.0)
Generalized weakness	3 (10.0)
Hypertension	2 (6.7)
Chest discomfort	2 (6.7)
Leukopenia	2 (6.7)
Transient ischemic attack	1 (3.3)
Dyspnea	1 (3.3)
Diarrhea	1 (3.3)
Decreased appetite	1 (3.3)
Palpitations	1 (3.3)
Fluid retention	1 (3.3)
Lightheadedness	1 (3.3)
Aura/flashing lights	1 (3.3)
Increased Raynaud activity	1 (3.3)
Acute kidney injury	1 (3.3)
Hyperkalemia	1 (3.3)
Hypokalemia	1 (3.3)
Transaminitis	1 (3.3)
Reason IVIG discontinued***, n (%)	
Improvement**	18 (60.0)
Stable**	4 (13.3)
Insurance denial	2 (6.7)
Progressing**	1 (3.3)
Aseptic Meningitis	1 (3.3)
Transient ischemic attack	1 (3.3)
Patient moved out of the country	1 (3.3)
Death	1 (3.3)

* No patients were receiving concomitant therapy with azathioprine, D-penicillamine, minocycline, colchicine, leflunomide, or TNF inhibitors. ** These were defined by the treating physician's clinical judgment. *** One patient was continuing to receive IVIG at the time of our study. IVIG: intravenous immunoglobulin; TNF: tumor necrosis factor.

patients from baseline to 12 months. There was, however, a borderline improvement in muscle severity (p = 0.054) from baseline to 12 months. Among the 5 patients with concomitant myositis, serial CK data were available in 4 patients, all of whom demonstrated normalization of CK over time (data not shown).

Treatment adverse effects and reasons for discontinuation of therapy. The most common adverse effects reported were headache (40%), fatigue (23.3%), nausea with or without emesis (13.3%), fever (10%), arthralgias and/or myalgias (10%), rash and/or pruritus (10%), and generalized weakness (10%; Table 2). One patient developed aseptic meningitis and ultimately discontinued IVIG because of severe side effects, 1 patient discontinued therapy because of a transient ischemic attack, and 1 patient developed an acute renal injury 15 months after discontinuing IVIG because of improvement. As detailed above, over 70% of patients discontinued IVIG based on improvement or stabilization as assessed by the treating physician. Two patients could not continue therapy because of insurance coverage issues. One patient died of sudden cardiac arrest from a preexisting cardiomyopathy 16 months after initiating IVIG.

Comparison of changes in mRSS to data from the relaxin study at 6 months. There were no differences in baseline characteristics between the IVIG cohort and the relaxin group (Table 1). The mean baseline mRSS of our IVIG cohort (29.6, SD 7.2) was not statistically significantly different from that of the relaxin group (mean 27.3, SD 6.9, p = 0.09). At 6 months, the mean change in mRSS was not significantly different between the IVIG (mean change –5.3, SD 7.9) and relaxin groups (mean change –4.8, SD 6.99; p = 0.74).

Comparison of changes in mRSS to data from the D-pen and collagen studies at 12 months. The IVIG cohort had a significantly longer disease duration at drug initiation (mean 24.6 mos, SD 19.9) relative to the D-pen subjects (mean 9.5 mos, SD 4.1, p < 0.0001) and a shorter disease duration compared to the collagen population (mean 41.8 mos, SD 31.9, p = 0.005). While the IVIG cohort had a racial profile comparable to the collagen group, the IVIG cohort had more whites and fewer blacks than the D-pen study (Table 1). There was no difference in age or sex profiles between the IVIG cohort and either study population. The mean baseline mRSS of our IVIG cohort (mean 29.6, SD 7.2) was significantly greater than that of the D-pen (mean 21, SD 8, p < 0.0001) and collagen trial groups (mean 26.1, SD 7.8, p = 0.023). At 12 months, the mean change in mRSS was statistically significantly better in the IVIG-treated cohort (mean change –8, SD 8.3) than the D-pen (–2.47, SD 8.6, p = 0.005) and collagen groups (–3.4, SD 7.12, p = 0.005).

Comparison of changes in mRSS to data from the MMF study at 6 and 12 months. There were no differences in baseline age, disease duration, sex, race, or disability between the IVIG and MMF groups. There were more patients with a concomitant myositis in the IVIG cohort than in the MMF group (p = 0.004), and the mean baseline mRSS was statistically significantly higher in the IVIG cohort (mean 29.6, SD 7.2) than in the MMF cohort (mean 24.5, SD 9.5, p = 0.009; Table 1). It is important to note that IVIG was typically used in patients who had not responded to other therapies, including a significant proportion of patients deemed MMF failures, and therefore these patients were considered to have more aggressive skin disease. At 6 months, there was a comparable improvement in the mean change in mRSS in the IVIG (mean –5.3, SD 7.9) and MMF cohorts (mean –3.4, SD 7.4, p = 0.256). Similarly at 12 months, the 2 groups had similar improvement in mRSS (IVIG mean change –8, SD 8.3; MMF mean change –7.1, SD 9, p = 0.674).

DISCUSSION

In our study, we sought to report our experience using IVIG in patients with severe, and often refractory, active dcSSc. We present one of the largest series describing the use of IVIG for this indication. Given the active and progressive nature of their skin disease, patients often were treated with IVIG in combination with other immunomodulatory or antifibrotic therapies. A significant improvement was noted in skin thickening over time, and comparison to historical controls from negative clinical trials with 12-month followup data suggests that this improvement may be greater at 12 months than what would be expected by the natural history of the disease. In addition, the cohort treated with IVIG had a clinical improvement in mRSS that was similar to a group of patients treated with MMF who were typically deemed clinical responders, suggesting that addition of IVIG may stabilize previously refractory disease. Over 50% of the IVIG-treated patients had a decline in mRSS of at least 5 points at the 6- and 12-month time intervals, and prior data suggest that these are clinically significant improvements[6]. While statistically significant improvements in HAQ-DI (which measures both activity and damage) were not observed, patients' assessments of disease severity significantly improved over time. In addition, 7 of the 10 patients with TFR at baseline had resolution of their TFR. Patients also remained stable with respect to pulmonary function and organ involvement while receiving IVIG treatment. We found IVIG to be well-tolerated, and the main reason (73.3% of patients) for discontinuing therapy was clinical improvement or stability as deemed by the treating physician. These data provide supportive evidence that IVIG may be beneficial in treating diffuse cutaneous disease in SSc, and a prospective, double-blind, randomized, placebo-controlled clinical trial is currently under way to further assess the efficacy of IVIG in SSc (NCT01785056).

We acknowledge that a majority of the patients in our

cohort were treated with MMF in conjunction with IVIG, often because they had failed therapy with MMF or other immunosuppressive agents. A comparison between our refractory cohort (the IVIG group) and a group of patients treated with MMF alone demonstrated comparable improvements in mRSS. We had expected that comparing our IVIG group who had refractory disease to a group of primary MMF responders would bias our findings to the null. Therefore, the finding that the IVIG cohort patients had an equivalent improvement in mRSS to the primary MMF responders suggests that IVIG, when used as an add-on therapy, may improve the responsiveness to treatment in patients with severe disease who are otherwise unresponsive to MMF alone.

Our study is not the first to anticipate the role of IVIG in treating fibrosis of the skin. Some reports suggested anecdotal benefit of IVIG therapy in individual patients[8,9,10], and other studies reported improved mean skin scores in small populations ranging from 3–15 patients[11,12,13,14,15]. To our knowledge, only 2 placebo-controlled studies have been conducted to date. Kudo, *et al*[16] reported the results of a 6-patient clinical trial of IVIG in patients with SSc showing changes in cytokine levels with no report of clinical outcomes. Another study by Takehara, *et al*[17] reported the use of IVIG in a randomized, double-blind, placebo-controlled trial of 63 patients with diffuse SSc. In this trial, participants were administered a single cycle of IVIG or placebo infusions. At 12 weeks, there were no differences in change in mRSS between the 2 groups. Participants whose skin score did not improve by at least 5 points at 12 weeks were given an additional cycle of IVIG. Those who received 2 IVIG treatments had greater improvements in skin score over time than those who initially received placebo followed by a later IVIG infusion. These data suggest that repeated IVIG cycles may influence longterm cutaneous outcomes. Our study, which evaluated patients receiving several monthly cycles of IVIG as part of routine clinical care, supports this idea.

Given the retrospective nature of our study, the lack of a placebo control, and the frequent use of concomitant immunosuppressive therapies, we cannot definitively attribute the improvement in skin thickening over time to the use of IVIG alone. To address these concerns, we compared the change in mRSS in our cohort to data from 3 large, negative randomized clinical trials to assess whether the improvements we detected were better than those expected from the natural history of the disease. It is important to note that our cohort had a few differences in baseline characteristics compared to these negative trials, particularly with respect to more severe skin disease at baseline and an intermediate disease duration at drug initiation compared to the D-pen and collagen studies. We recognize that patients with higher baseline skin scores in clinical trials tend to improve, whereas patients with less severe cutaneous disease tend to worsen[18]. Participants of the relaxin trial were the most similar to our IVIG cohort at baseline. We did not see differences between our IVIG cohort and the relaxin study at 6 months, and unfortunately 12-month outcome data were not available for comparison.

These data suggest that IVIG may be a beneficial adjunctive therapy for patients with active dcSSc who are unresponsive to more traditional immunosuppressive treatments, but further studies are necessary to affirm these findings.

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APPENDIX 1. Sensitivity analyses methods.

For our primary analyses, we examined baseline modified Rodnan Skin score (mRSS) up to 3 months before intravenous immunoglobulin (IVIG) initiation. We therefore performed sensitivity analyses to examine whether restricting the baseline mRSS data to a more stringent criterion (up to 2 mos prior to IVIG initiation) changed our results. We also performed sensitivity analyses examining whether restricting forced vital capacity, DLCO, Health Assessment Questionnaire-Disability Index, tendon friction rubs, and Medsger severity scale data to tighter time intervals (up to 3 mos prior to IVIG initiation for baseline, 12 ± 3 mos for timepoint 2) changed our results.

APPENDIX 2. Sensitivity analyses results.

Sensitivity analyses were performed to examine whether restricting the baseline modified Rodnan Skin score (mRSS) to ≤ 2 months prior to intravenous (IVIG) initiation changed our findings. Within the IVIG cohort, there was a progressive reduction in mean mRSS over time, which was unchanged compared to our primary analysis (data not shown). When sensitivity analyses were performed in the IVIG cohort restricting pulmonary function test, Health Assessment Questionnaire-Disability Index, and Medsger severity scale data to tighter intervals around baseline and 12 months, the results were unchanged (data not shown). The improvement in muscle severity scores from baseline to 12 months remained borderline ($p = 0.08$). We also examined whether tendon friction rubs (TFR) improved within the first 6 months of initiating IVIG. When we restricted our descriptive analysis to patients who had known TFR 0–3 months prior to IVIG initiation, 6 patients were found to have TFR at baseline, only 1 of whom continued to have TFR at the 6-month timepoint.