SUSTAINED BENEFIT FROM INTRAVENOUS IMMUNOGLOBULIN THERAPY FOR GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Running title: IVIG therapy in GI involvement in SSc

ABSTRACT

OBJECTIVE: Intravenous immunoglobulin (IVIG) is known to confer significant benefit in rheumatological conditions including inflammatory myopathy. This study is aimed to assess efficacy of IVIG across different aspects of internal organ involvement in refractory active systemic sclerosis (SSc) particularly the gastrointestinal system.

METHODS: SSc patients with overlap polymyositis who remained active and unresponsive to conventional disease-modifying agents and who subsequently received IVIG were identified. Gastrointestinal symptoms were assessed using validated questionnaires. Medical Research Council (MRC) Sum Score for muscle strength and Modified Rodnan Skin Score (mRSS) were assessed. Serial measurements were undertaken at baseline prior to first IVIG and post treatment in the most recent assessment.

RESULTS: Fifteen SSc patients were consecutively recruited into this observational study. Mean duration of IVIG treatment was 2.3 years with treatment frequency ranging from 6 weekly to 4 monthly. Compared to baseline, there was significant reduction in gastro-oesophageal reflux frequency and intensity mean scores ($p=0.006$ and $p=0.013$, respectively). Significant improvement in GIT 2.0 score from baseline mean score (±SD) 1.07 ± 0.67 to 0.60 ± 0.46 ($p=0.002$) was observed. There was regression in markers of muscle disease with reduction in mean (±SD) MRC Sum Score and median creatine kinase level ($p=0.001$ and $p=0.025$, respectively). Significant amelioration of mean basal mRSS (±SD), 21.5 ± 13.8 to 10 ± 10.6 ($p=0.005$) was observed.

CONCLUSION: IVIG may be a helpful adjunctive therapy in amelioration of some key clinical aspects in refractory SSc. Sustained benefit from IVIG suggests specific immunomodulatory effect on those with established SSc gastrointestinal complications.

Key words: Systemic sclerosis; Intravenous immunoglobulin; gastrointestinal manifestation; myositis; refractory

KEY MESSAGES

1) Long-term IVIG therapy provides benefit in amelioration of some key clinical aspects in refractory SSc.

2) SSc patients with both upper and lower gastrointestinal manifestations had significant improvement with IVIG therapy.
3) Our data supports potential benefit for immunomodulation with IVIG therapy in established SSc gastrointestinal complications.

INTRODUCTION

~~Systemic sclerosis (SSc) is an uncommon autoimmune rheumatic with the pathological hallmark of fibrosis with excessive collagen deposition and accumulation in skin and internal organs [1]. The treatment of SSc using immunotherapies is targeted towards managing the organ based complications, mainly by alteration of vascular and fibrotic damage secondary to immune activation, which is central to SSc pathogenesis.~~The treatment of systemic sclerosis (SSc) using immunotherapies is targeted towards managing organ based complications. ~~A~~ A number of cytotoxic agents and immunomodulatory therapies are used in the treatment of SSc ~~The organ-based treatment using immunosuppressive agents is aimed to be started as early as possible to slow down the disease progression and to reduce the severity of the complications~~. ~~A number of cytotoxic agents and immunomodulatory therapies are used in the treatment of SSc include cyclophosphamide, methotrexate, mycophenolate mofetil (MMF) and autologous hematopoietic stem cell transplantation [2-4]. These immunotherapies are being used~~ with varying degrees of efficacy and with inconsistent results, with some patients being refractory to these conventional approaches [2-4].. ~~Balancing potential clinical benefit with the known risks of immunosuppression is an important aspect of management.~~ The use of IVIG in SSc has been evaluated mostly in case series and small uncontrolled studies, particularly assessing the improvement in skin fibrosis

and inflammatory myopathy overlap in SSc [9-14]. It is generally considered a safe immunomodulatory therapy in routine use for a wide range of immune-mediated conditions [6-8].

~~Intravenous immunoglobulin (IVIG) contains pooled, polyvalent IgG antibodies extracted from plasma from more than 10,000 blood or plasma donations [5]. It is generally considered a safe immunomodulatory therapy in routine use for a wide range of immune-mediated conditions, such as idiopathic thrombocytopenic purpura, immunobullous diseases and chronic inflammatory demyelinating polyneuropathy [6-8]. The use of IVIG in SSc has been evaluated mostly in case series and small uncontrolled studies, particularly assessing the improvement in skin fibrosis [9-12]. It is also known to have beneficial effects in rheumatological conditions with inflammatory myopathy including myositis overlap in SSc [13, 14].~~ Given the heterogeneity of the various ~~rheumatological and neurological~~ diseases that respond to IVIG, it is probable that different autoimmune-related specific pathways mediate the efficacy of this treatment for each disease.

~~There are few postulated mode of actions of IVIG in SSc. One of them is by i~~Inhibition of effector function of activated T cells and released cytokines, complement pathway inhibition, Fcγ receptor blockade and immunomodulation of lymphocyte differentiation are few postulated mode of actions of IVIG in SSc [15-19]. ~~or on its competition with MHC molecules. N~~Neutralization of circulating autoantibodies by antibodies in immunoglobulins is also ~~is also~~ believed to take place. ~~Others include complement pathway inhibition, Fcγ receptor blockade or induction of inhibitory Fcγ receptor on the surfaces of macrophages and B cells by IgG binding, immunomodulation of lymphocyte differentiation and cytokine synthesis [15-19].~~ Another possible explanation of ~~the beneficial effect of~~ IVIG effect on

fibroblasts is by blocking the activity of Fas through inhibition of fibrogenesis, by ~~the~~ presence of anti-Fas antibodies in the IVIG preparations [20].

Gastrointestinal (GI) involvement in SSc is frequent [21] and can be severe with some patients having ~~the most common manifestation in SSc, seen in up to 90% of the patients [21]. One of the major comorbidities associated with SSc is GI disease that may result in severe~~ life-threatening complications with pseudo-obstruction, malabsorption and malnutrition. ~~in some cases.~~ Considering the limited evidence available to suggest potential benefit of IVIG in SSc and recent case reports that suggested improvement in the GI aspect of SSc that is typically refractory to other putative disease modifying treatment [9, 10, 22-24], this present study aims to assess the efficacy of IVIG across different aspects of internal organ involvement in refractory active SSc, particularly the GI complication. ~~of the disease.~~

PATIENTS AND METHODS

All subjects included in this study were recruited from Centre for Rheumatology and Connective Tissue Diseases at the Royal Free Hospital with clinical information recorded and collected between March and November 2014. The study was approved by the London-Hampstead NRES Committee (~~Project~~ reference no: 6398) and ~~was~~ in compliance with the WMA Declaration of Helsinki 2013. Fifteen SSc patients who remained unresponsive to standard disease-modifying agents and subsequently received IVIG treatment on a regular infusion basis were identified from the large cohort of more than 1400 SSc cases attending our centre. All subjects fulfilled the 2013 EULAR/ American College of Rheumatology criteria of SSc [25]~~.~~and ~~i~~informed consent to participate in the study was obtained. ~~from all subjects.~~

The 15 SSc patients recruited were receiving IVIG treatment for inflammatory myopathy and judged not to have achieved satisfactory clinical response to conventional immunosuppressive agents.

~~Medical record review~~

~~Demographic, clinical and laboratory details were obtained from medical records review. The subjects were classified as having either limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc). They were assessed at regular intervals either during their outpatient appointments or at the time of IVIG treatment in our day care unit or inpatient admissions. The presence of the following clinical features was determined: Raynaud's, digital ulcer, calcinosis, history of scleroderma renal crisis, lung fibrosis (extent of lung fibrosis >20% on high resolution CT thorax with FVC <70%), pulmonary arterial hypertension (PAH), cardiac involvement (direct cardiac involvement or secondary to PAH, lung fibrosis or kidney disease) and myositis [26, 27].~~ Serial assessments of the following internal organ involvement or clinical manifestation were undertaken at baseline prior to IVIG treatment and post IVIG treatment.

Assessment of gastrointestinal symptoms

The upper and lower gastrointestinal symptoms were assessed using two validated questionnaires, the Reflux Disease Questionnaire (RDQ) and UCLA SCTC GIT 2.0 questionnaire, which were self-administered [28-30]. ~~The RDQ has been validated for its utility in diagnosing gastro-oesophageal reflux disease (GORD) while the UCLA SCTC GIT 2.0 instrument has been validated for the use in SSc-associated GI involvement with good test-~~

~~retest reliability.~~ These questionnaires were used for assessment of symptoms prior to receiving the first IVIG infusion and the current symptoms while on IVIG treatment.

The UCLA SCTC GIT 2.0 questionnaire consists of seven items ~~in which frequencies were assessed in five categories of symptoms~~: reflux, distension, faecal soilage, diarrhoea, ~~and~~ constipation, ~~; and the effects of symptoms on two categories:~~ social functioning and emotional well-being. The number of days affected by these symptoms during the previous week was evaluated ~~(divided in four scales: 0 days, 1-2 days, 3-4 days and 5-7 days)~~. The average score for each category was calculated and the average total score for all categories were then determined. All the items other than constipation were used in the score. ~~Patients were instructed to provide the best answer they can even if they are unsure how to answer a question.~~

~~In addition,~~ RDQ was specifically used to assess gastroesophageal reflux disease (GORD). ~~gastroesophageal reflux disease (GORD).~~ It ~~consists of 6 components that~~ evaluates the frequency and intensity of three domains (heartburn, regurgitation and dyspepsia) during the previous week. ~~Each domain consists of two components. For each component, rating was given by patient with s~~Score rang~~ed~~ing from 1 to 6 for frequency (not present to daily) and severity (not present to severe). The mean score for each domain, RDQ frequency and ~~RDQ~~ intensity was calculated. The higher scores indicate more frequent or severe ~~severe or frequent~~ symptoms.

Assessment of muscle strength

Total Medical Research Council (MRC) Sum Score for muscle strength was evaluated and calculated (0 to 60). ~~prior to receiving IVIG and post IVIG treatment. A scale 0 to 5 assesses the power of shoulder abductors, flexors of the elbow, hip and ankle, and extensors of the wrist and knee. A total motor power score was calculated (MRC sum, 0 to 60).~~

Assessment of skin fibrosis

The extent of skin fibrosis was assessed using the modified Rodnan Skin Score (mRSS). Serial mRSS prior to IVIG and available serial readings performed at end of each cycle were assessed, including the current assessment.

Assessment of lung

FVC and DLCO (predicted %) were evaluated from lung function tests done. ~~prior to first IVIG treatment and available serial readings while on IVIG treatment.~~

Statistical analysis

All analyses were performed using SPSS version 19. Pearson and Spearman correlation test, Pearson chi-square, ~~test and~~ Fisher exact ~~test~~ and Student's T test were performed where appropriate to test the associations and ~~between categorical variables while the Student's T-test was used~~ to compare ~~continuous~~ variables. $p \leq 0.05$ was considered as statistically significant. ~~Pearson and Spearman correlation were used for assessment between disease~~

~~duration at IVIG initiation, duration of IVIG therapy, SSc disease duration and the response status at the end of the study.~~

RESULTS

Clinical characteristics of SSc patients

~~The majority of patients were females (87%). Eleven (73.3%) patients had dcSSc.~~ The clinical charecteristics, IVIG treatment details and other treatment received for each patient were summarised in Table 1. Mean (±SD) age was 47.3 ± 12 years. Mean (±SD) disease duration from onset of first non-Raynauds symptoms was 7 ± 3.9 years. Mean duration of IVIG treatment was 2.3 years (range 3 months to 11 years), with treatment frequency ranging from 6 weekly to 4 monthly. All 15 patients received IVIG treatment for indication of inflammatory myopathy, based on Peter and Bohan criteria [26, 27]. One patient received IVIG for indication of chronic intestinal pseudo-obstruction in addition to inflammatory myopathy. ~~Three (20%) patients were positive for anti-ScL-70, another 3 (20%) for anti-RNA Polymerase III antibody, while none of the patients had positive anti-centromere or PM-ScL antibody. The others had positive antibody for SSA and SSB (one patient), nRNP (one patient), U3 RNP (one patient), PL-7 (one patient) and Jo-1 (2 patients). The remaining 3 patients were negative for ENA testing. The 3 patients with PL-7 and Jo-1 antibodies had cytoplasmic staining pattern in ANA. Five (33.3%) patients had lung fibrosis, 4 (26.6%) patients had cardiac involvement, one had past history of renal crisis and none had PAH.~~ All patients were maintained on standard and optimal doses of proton-pump inhibitors (PPI), histamine H2 receptor antagonist or prokinetic agents with or without in combination since prior to initiation of IVIG. They also received immunosuppressive agents of standard dose.

~~14 patients received oral prednisolone. Nine patients were on MMF with the median dose of 1500 mg daily, while in another 5 patients MMF was stopped. Nine patients were on methotrexate, whereby in 6 out of these 9 patients methotrexate was later stopped. MMF and methotrexate were stopped in these patients due to adverse reactions such as leukopenia, liver impairment, GI side effects, varicella zoster and recurrent soft tissue infections; except for two patients where the immunosuppressive agents did not seem to be efficacious. Three patients were on hydroxychloroquine. Seven patients had previously received intravenous cyclophosphamide pulses.~~

Assessment of internal organs following treatment with IVIG

Assessment of ~~upper~~ GI symptoms ~~using RDQ~~

The mean values of frequency and intensity for GORD and each domain in the RDQ assessment~~, (heartburn, dyspepsia and regurgitation), pre- and post IVIG treatment were shown in Table 1.~~GIT 2.0 ~~-~~average score of each category and the average total score from all categories, both pre- and post IVIG treatment were shown in Table 2. ~~Compared to baseline, there was significant improvement in GORD frequency mean scores (p=0.006). Significant improvement was also observed in GORD intensity mean scores (p= 0.013). For each domain, significant improvement was also seen.~~

~~*Assessment of upper and lower GI symptoms using UCLA SCTC GIT 2.0 questionnaire*~~

~~The average score of each category (reflux, distension, faecal soilage, diarrhoea, social functioning and emotional well-being) and the average total score from all categories were shown in Table 2. GIT 2.0 score improved significantly from baseline mean score (±SD) 1.07 ± 0.67 to 0.60 ± 0.46 (*p*=0.002). Significant improvement was also observed in all the above categories except for faecal soilage.~~

One patient with chronic intestinal pseudo-obstruction had improvement in abdominal distension, diarrhoea, malabsorption, ~~and~~ electrolyte imbalance and feeding regime after receiving IVIG. ~~With IVIG treatment, the patient no longer received feeding via naso-jejunostomy tube; and the frequency of total parenteral nutrition (TPN) was reduced from 7 days per week to four days per week.~~

Assessment of myopathy

Mean (±SD) baseline MRC Sum Score was 51.7 ± 3.6, which increased to 56.5 ± 2.9 (*p*= 0.001) at the end of the study. Baseline median creatine kinase level was 192 (range 35 to 3192) with significant reduction to 77 (range 42 to 465) (*p*=0.025). ~~An EMG study in one patient showed active myositis prior to first treatment of IVIG, with documented improvement on subsequent EMG with reduced inflammatory potentials following the third course of IVIG given six weeks apart between each course. Repeat EMG was not undertaken for the remaining patients.~~ IVIG conferred a steroid-sparing effect in 8 out of 13 (61.5%) patients. The median dose reduction in oral prednisolone was 8.75 mg (range 2.5 to 17.5 mg). ~~The f~~Frequency of IVIG treatment was reduced in all except in two patients, due to

improvement and stability of myopathy. These patients' IVIG frequency was reduced from the initial 4 weekly regime, gradually to 6 weekly, 8 weekly, 3 monthly or 4 monthly.

Assessment of skin fibrosis

There was significant amelioration of mean basal mRSS (±SD), 21.5 ± 13.8 to 10 ± 10.6 (p=0.005 at post-treatment). ~~Mean basal mRSS assessment was undertaken at 1.5 years prior to IVIG initiation (range 3 months to 5 years), while post treatment assessment was performed at 3.4 years (range 3 months to 11 years).~~

Other assessments

No improvement in lung function parameters~~, FVC and DLCO~~ was observed. Four out of seven patients with digital ulcers ~~(57.1%)~~ reported ~~reduction in frequency of digital ulcers with~~ no new digital ulcers in response to IVIG treatment. All seven patients were on oral vasodilator treatment for Raynaud's, including five~~with 5 out of 7 patients~~ on Iloprost infusion~~. treatment. Improvement and/or resolution of subcutaneous calcinosis were reported in 3 out 5 (60%) patients.~~ Disease duration at IVIG initiation, duration of IVIG therapy and SSc disease duration were not associated with the response status at the end of the study.

DISCUSSION

This observational study on a limited number of SSc patients with refractory inflammatory myopathy shows that IVIG improved various clinical aspects including GI disease, myopathy and skin fibrosis. ~~Interestingly, o~~Our patients reported improvement in GI symptoms after receiving IVIG treatment despite maximal gastro-protective and prokinetic agents. As there is no evidence to suggest an immunomodulatory effect of currently available DMARDs on GI disease in SSc, the current approach of management focuses on symptomatic relief and supportive treatment with medication, diet modification, nutritional support and occasionally surgical treatment in severe refractory cases. Therefore this promising observation suggests that IVIG may be useful in a subset of SSc patients with severe and debilitating GI disease.

Although individual cases have been reported~~, including two patients from our centre~~ [24], this is the first study to systematically assess the impact of IVIG treatment in the GI system in SSc in a well characterised disease cohort, and to explore longer term outcomes in extended follow-up. ~~Both upper and lower GI involvement of SSc patients in the current study had significant improvement with IVIG therapy in each domain except for faecal soilage, in the two validated disease-specific GI outcome measures. Specifically, each of the key components of RDQ demonstrated improvement in heartburn, dyspepsia and regurgitation.~~ There were significantly lower scores~~, in response to IVIG treatment,~~ for each key component of RDQ and ~~all the items in the~~ UCLA SCTC GIT 2.0 questionnaires ~~, including reflux, abdominal distension, diarrhoea and emotional well-being, with~~ including a positive trend observed for faecal soilage .~~(P=0.059).~~ One patient had improvement in manifestations of chronic intestinal pseudo-obstruction following IVIG treatment. ~~Few case reports in literature reported r~~Resolution of ~~the~~ pseudo-obstruction secondary to various

autoimmune conditions after IVIG administration was previously reported~~of IVIG~~ [31, 32]. ~~The use of IVIG has also been reported to be beneficial in polymyositis and dermatomyositis patients with severe life-threatening oesophageal disorders [33].~~

The pathophysiology of GI abnormalities in SSc is not well understood, but is contributed to both myogenic and neurogenic factors~~, as a consequence of initial vascular damage, leading to inflammation, excessive collagen deposition in the submucosa and smooth muscle atrophy~~ [34, 35]. Immunological abnormalities are also implicated in its pathogenesis, for example over-expression of profibrotic factors such as transforming growth factor-β (TGF-β), endothelin-1 and connective tissue growth factor [36]. The end result is impaired peristaltic activity with various secondary problems such as GORD, delayed gastric emptying, ~~early satiety, abdominal distension,~~ small intestine bacterial overgrowth, incontinence and pseudo-obstruction~~, leading to malabsorption and malnutrition~~. It is not known how IVIG works in improving the GI symptoms in SSc patients. Given the potential benefit IVIG has on skin and inflammatory myopathy [9,14~~-11-14, 37, 38~~], it is likely that IVIG possibly works in a similar way in the GI tract. In SSc fibroblasts, it is postulated that the increased fibrotic tissue is due to overexpression of various growth factors including interleukin-4 (IL-4) and TGF-β [39-42]. ~~In addition to these profibrotic cytokines,~~ SSc fibroblasts also express excessive α-smooth muscle actin (α-SMA) and type 1 pro-collagen and less matrix metalloproteinase-1 (MMP-1)[38]. In an experimental study by Blank *et al* in which IVIG was administered to tight skin mice, the effect on the profibrotic cytokines was observed with downregulation of type 1 pro-collagen with decreased collagen deposition [43]. The inhibitory effect on IL-4 and TGF-β was also reported following administration of

IVIG [38, 43]. IVIG is also known to have a regulatory effect on MMP, thus potentially promoting tissue repair [46].

Similarly, high amount of collagen type I and III in the lamina propria that increased towards the muscularis mucosae were demonstrated on gastric samples from SSc patients ~~with SSc~~. ~~In addition, t~~Type IV collagen was present around the glands and small vessels of mucosa, and this may lead to alteration in secretory function and vascular tone dysfunction. Strong expression of several profibrotic factors such as TGF-β and myofibroblasts with increased α-SMA were also observed in the gastric samples which might account for the increased extracellular matrix synthesis and deposition [36].

~~In an experimental study by Blank *et al* in which IVIG was administered to tight skin mice for four weeks (total dose: 2gm/kg), the effect on the profibrotic cytokines was observed with downregulation of type 1 pro-collagen with decreased collagen deposition [43]. The inhibitory effect on IL-4 and TGF-β was also reported following administration of IVIG [38, 43]. In another study, both the affected sera and skin of SSc patients had increased expression of IFN-γ and IL-12 after receiving IVIG treatment, suggesting a rebalance of downregulated Th1 cytokines in SSc patients [44]. On the other hand, IVIG partially abrogated TGF-β production by downregulation of T cells or by direct binding of IVIG to TGF-β in a study conducted in patients with dermatomyositis [45]. The authors also reported reduced local expression of TGF-β in the muscles of patients who responded favourably to IVIG. IVIG is also known to have a regulatory effect on MMP; which are extra-cellular matrix proteases enzymes, thus potentially promoting tissue repair [46].~~

In the GI tract, the intrinsic neurons in the myenteric plexus have an important role in the contractile activity, with acetylcholine as the principle excitatory neurotransmitter acting via

the antimuscarinic-3-acetylcholine receptor (M3R). Interestingly, antibodies against M3R were recently described in SSc patients with severe GI, suggesting a potential link with dysmotility in SSc [47]. Another study identified presence of specific SSc IgG-M3R complex on the smooth muscle cells of internal anal sphincter of rats. The immunoglobulins from SSc patients resulted in significant inhibition of the M3R, which was reversible with antibody removal. The authors suggested that SSc GI dysmotility may be caused by autoantibodies blocking the muscarinic neurotransmission in the smooth muscle cells. Therefore a treatment directed towards neutralization or removal of those antibodies may benefit the SSc patients [48].

~~Some previous studies report possible efficacy of IVIG for skin sclerosis in SSc patients [9, 11, 12, 23, 38].~~ The effect of IVIG therapy was confirmed by improvement in the skin score ~~(mRSS)~~ and histological examination of SSc skin samples ~~-~~[11, 38]. ~~The positive results from IVIG treatment was also further observed in skin samples of bleomycin-induced SSc murine model, demonstrating downregulation of monocyte chemoattractant protein (MCP-1/CCL2) and TGF-β production [49]. One randomized, double–blind, placebo-controlled~~ A trial ~~involving 63 SSc patients~~ demonstrated significant improvement in skin score in patients receiving two courses of IVIG compared to patients receiving a single course, ~~. There was significant difference at week 60 with improvement in minimally important difference (MID) estimates for mRSS,~~ suggesting that multiple-course treatment over a specific duration may be critical to assess efficacy of IVIG [10]. Our data is consistent with the reported results with reduction in skin score ~~by 11.5 ± 3.2~~ with repeat cycles of IVIG course.

Importantly, clinical improvement in inflammatory myopathy following IVIG treatment was demonstrated in our patients~~, which is~~ consistent with other reports [37, 50]. ~~In this current~~

~~study t~~The MRC sum score improved following each cycle of IVIG received, in addition to a cumulative improvement in the score from the baseline of first cycle of IVIG. As the effect of IVIG weaned in varying degrees in some patients, the courses of IVIG were administered at an appropriate time to maintain response. Over time, the frequency of IVIG courses was reduced in almost all patients as the disease stabilised. A minority of the patients noted ~~a~~ subjective improvement in their digital ulcers following IVIG therapy, which may be accounted by remodelling of the microvasculature pathology and fibrotic microenvironment, eventually promoting the healing of ulcers.

~~The number of studies involving IVIG treatment in SSc is restricted largely to case reports.~~ There is currently no evidence that IVIG therapy halt the progression of GI disease in SSc. IVIG, however was well tolerated in all of our patients without any significant side effects. There are several limitations in this study. This study was not originally designed to assess the effect of IVIG in GI manifestations; instead IVIG was administered for refractory inflammatory myopathy.~~Our patients received variable numbers of repeat cycles of IVIG at various time intervals; thus we did not perform objective assessments at specific time intervals.~~ We did not have SSc patients without myositis on IVIG treatment, therefore it remains a matter of speculation whether the pathogenetic mechanisms underlying GI involvement in the patients, partly might be related to myositis-specific pathogenetic process itself and therefore could be more responsive to IVIG.~~Another drawback is that using a subjective symptom questionnaire may not accurately describe actual disease severity; therefore disease activity may have been underestimated.~~ However, despite a small sample size, our study has shown positive encouraging results in various SSc clinical manifestations.

CONCLUSION

This study provides support that IVIG use is associated with improvement of clinical features in SSc patients who have been refractory to other immunosuppressive therapies. This approach warrants further prospective evaluation in a controlled trial and also suggests a specific potential benefit for immunomodulation in established gastrointestinal complications.

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Table 1. Demographic, clinical characteristics and treatment details of each patient

Patient	Age at study entry	Age at IVIG initiation	Gender	Subset	Autoantibodies	Organ involvement	Duration of GI symptoms (years)	Duration of IVIG treatment (months)	Duration of SSc at IVIG initiation (years)	GI medications	Immunosuppressants received		Lab values		
											Previous	Current	Hb (g/L)	Alb (g/L)	CRP (mg/L)
1	19	18	F	L	SSA, SSB	none	4	18	3	L	MTX, infliximab	MMF, HCQ, pred	10.3	43	2
2	54	53	M	D	ScL 70	cardiac SSc	5	13	4	L,R,D	MMF, CYC	MTX, pred	13.3	44	6
3	29	27	F	D	ScL 70	none	4	31	2	L,D	MTX	MMF, pred	13.3	39	5
4	54	49	F	L	nRNP	PF	12	29	9	L,D	MMF,HCQ	pred	14.1	41	3
5	60	58	F	D	Jo-1	cardiac SSc	8	23	6	E,R,M,G	MTX,HCQ, CYC, CSA, AZA	MMF, pred	13.4	40	2
6	44	33	F	D	ScL 70	cardiac SSc, PF	12	135	2	L,R,D	CYC, aza	MMF, MTX, HCQ, pred	11.7	44	2
7	50	47	F	D	ANA +, ENA -	none	4	33	1	L,D	MMF	pred	9	43	1
8	53	45	F	D	RNAP	none	13	100	5	L,On,G	MMF, MTX, CYC, CSA, pred	none	11	48	6
9	46	45	F	D	RNAP	none	3	13	2	L,R	CYC	MMF, pred	10.8	42	9
10	54	53	M	D	U3RNP	cardiac SSc	5	3	5	L,R,M	CYC	MMF, pred	12.1	39	1
11	41	39	F	D	RNAP	none	4	14	3	Ra	MTX, AZA, rituximab	MMF, HCQ, pred	10.5	48	2
12	49	40	F	D	ANA +, ENA -	SRC	13	23	5	L,R	None	MMF, HCQ	11.7	49	1
13	43	42	F	L	PL-7	PF	5	3	5	O	CYC	MMF, pred	11	39	11
14	45	44	F	D	ANA +, ENA -	PF	3	3	3	O	MMF, tocilizumab	MTX, pred	13	38	5
15	69	68	F	L	Jo-1	PF	10	5	10	O	MTX, CSA	pred	11.9	40	5

Abbreviations:
Systemic sclerosis (SSc), intravenous immunoglobulin (IVIG), gastrointestinal (GI), Laboratory (lab) values - haemoglobin (Hb), albumin (Alb), c-reactive protein (CRP); Gender - male (M), female (F); Subset - limited cutaneous (L), diffuse cutaneous (D); Autoantibodies – ribonucleoprotein (RNP), anti-nuclear antibody (ANA), extra nuclear antibody (ENA), RNA Polymerase (RNAP); Organ complications - pulmonary fibrosis (PF), scleroderma renal crisis (SRC); GI medication – lansoprazole (L), esomeprazole (E), omeprazole (O), rabeprazole (Ra), ranitidine (R), gaviscon (G), domperidone (D), metoclopramide (M), Ondansetron (On); Immunosuppressants – mycophenolate mofetil (MMF), methotrexate (MTX), hydroxychloroquine (HCQ), cyclophosphamide (CYC), ciclosporin (CSA), azathioprine (AZA), prednisolone (pred)

Table 2 Results of Reflux Disease Questionnaire (RDQ) and UCLA SCTC GIT 2.0 questionnaire pre- and post treatment with IVIG

	Mean score (±SD)	*p* value (≤ 0.05)
RDQ		
GORD frequency pre-IVIG	3.19 ± 1.79	
GORD frequency post-IVIG	1.88 ± 0.90	0.006
Heartburn frequency pre-IVIG	2.83 ± 1.85	
Heartburn frequency post-IVIG	1.76 ± 0.99	0.021
Dyspepsia frequency pre-IVIG	3.16 ± 1.93	
Dyspepsia frequency post-IVIG	1.70 ± 0.97	0.008
Regurgitation frequency pre-IVIG	3.60 ± 1.81	
Regurgitation frequency post-IVIG	2.20 ± 1.16	0.007
GORD intensity pre-IVIG	3.03 ± 1.70	
GORD intensity post-IVIG	1.96 ± 0.86	0.013
Heartburn intensity pre-IVIG	2.73 ± 1.80	
Heartburn intensity post-IVIG	1.60 ± 0.71	0.016
Dyspepsia intensity pre-IVIG	2.80 ± 1.77	
Dyspepsia intensity post-IVIG	1.90 ± 0.91	0.035
Regurgitation intensity pre-IVIG	3.56 ± 1.79	
Regurgitation intensity pre-IVIG	2.40 ± 1.40	0.013
GIT 2.0 Questionnaire		
Total GIT 2.0 score pre-IVIG	1.07 ± 0.67	
Total GIT 2.0 score post-IVIG	0.60 ± 0.46	0.002
Reflux pre-IVIG	1.52 ± 0.92	
Reflux post-IVIG	0.88 ± 0.62	0.011
Distension pre-IVIG	1.86 ± 0.79	
Distension post-IVIG	1.08 ± 0.67	0.003
Soilage pre-IVIG	0.66 ± 0.89	
Soilage post-IVIG	0.33 ± 0.61	0.059
Diarrhoea pre-IVIG	0.73± 0.70	
Diarrhoea post-IVIG	0.36 ± 0.63	0.026
Social functioning pre-IVIG	0.85 ± 0.90	
Social functioning post-IVIG	0.59 ± 0.60	0.146
Emotional well-being pre-IVIG	0.79 ± 1.03	
Emotional well-being post-IVIG	0.39 ± 0.69	0.050

Patient	Total GIT 2.0 Score	
	Pre-IVIG (baseline)	Post-IVIG (end of study)
1	0.041	0.096
2	0.617	0.596
3	0.575	0.318
4	1.021	0.878
5	0.992	0.058
6	0.846	0.659
7	1.583	1.041
8	2.155	0.193
9	2.547	1.81
10	1.411	1.089
11	1.596	0.341
12	0.834	0.67
13	0.547	0.575
14	0.916	0.534
15	0.417	0.166