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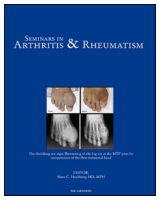

Role of intravenous immunoglobulins in systemic sclerosis (SSc): A systematic literature review

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ABSTRACT

Background: Systemic sclerosis (SSc) is a heterogenous, multi-system autoimmune disease that causes progressive fibrosis of the skin and internal organs, resulting in high morbidity and mortality. Intravenous Immunoglobulin (IVIG) is a therapeutic option for SSc; however, reports of its efficacy have been variable, and its use across multiple organ manifestations of SSc has not been comprehensively reviewed.
Aim: The aim of this study was to systematically assess the existing literature on the role of IVIG use across a range of SSc manifestations.
Methods: Medline, Embase, Cochrane, Web of Science and Scopus were searched from 01/01/2003–15/04/2024 using terms related to SSc and IVIG. Included studies were English-language full texts, where ≥5 adults with SSc received IVIG, and where a reportable outcome was documented.
Results: Of 418 potentially relevant records, 12 were included in this review, comprising 266 patients across one randomised control trial, two pilot studies, one open label study, seven retrospective studies and one case control study. Eighteen outcomes were documented across five different organ systems: cutaneous, respiratory, musculoskeletal, gastrointestinal, and other (clinical improvement and corticosteroid sparing benefit). Results showed a favourable effect of IVIG in reducing the extent of skin thickening, muscle and joint pain, gastrointestinal symptoms, steroid dosing and improving patient/physician reported quality of life. Whilst IVIG may appear to be less beneficial for respiratory disease, the stabilisation in pulmonary function tests and radiological features may be considered a positive outcome in itself. Limitations included a lack of high-quality studies, and the use of concomitant therapies in many studies, rendering the efficacy of IVIG alone difficult to ascertain.
Conclusion: IVIG showed benefit in treating some manifestations of SSc, however there was a lack of convincing evidence for the efficacy in others. The lack of high-quality data highlights the need for further well-designed clinical trials to confirm these findings and inform guidelines for IVIG use.

Introduction

Scleroderma or systemic sclerosis (SSc) is a multisystem autoimmune disease that though rare, affects 30–240 people/million worldwide, and is associated with significant morbidity and mortality [1]. Though incompletely understood, the pathogenesis of SSc is thought to result from both a genetic predisposition and environmental exposure that together dysregulate the immune system, leading to excessive collagen production and microvasculopathy. This results in progressive fibrosis of the skin and internal organs, leading to multiple disease manifestations [2,3].

SSc can be classified based on the degree of skin involvement. Limited cutaneous SSc (lcSSc) is characterised by thickening of skin on the face and that distal to the elbows and knees. The diffuse form (dcSSc) has more extensive involvement, affecting skin proximal to the elbows and knees, and conveys a poorer prognosis [4]. Other forms include sine scleroderma, where there is internal damage without cutaneous fibrosis, and SSc-overlap syndromes, which carries features of other connective tissue diseases (CTDs) [5].

Current SSc management relies predominantly on treatments

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conferring symptomatic benefit for a particular manifestation, such as calcium channel blockers for Raynaud's phenomenon [2]. Recently, there has been increasing interest in immunomodulatory therapies, including biological agents such as rituximab [5], in addition to corticosteroids, methotrexate, azathioprine and mycophenolate mofetil (MMF) [6]. Due to the heterogenous nature of SSc and many SSc-overlap syndromes, the success of investigated agents has been variable [4], and an effective therapeutic strategy targeting fibrogenesis remains elusive [7].

Intravenous Immunoglobulin (IVIG) is human IgG derived from the pooled plasma of healthy blood donors. Originally used as the gold-standard therapy for immunodeficiencies, its application has since expanded due to the proven immunomodulatory properties of IgG-Fc (fixed chain) [6]. IVIG has already been shown to be a validated therapeutic option for various autoimmune diseases [8,9], such as myasthenia gravis, where its mechanism of action involves antibody neutralisation, inflammatory mediators inhibition, and B-cell surface Fc receptor blockade [4]. Additionally, it has a favourable side effect profile, mostly limited to mild symptoms, and most importantly, is not associated with an increased risk of infection, unlike conventional immunosuppressants [10].

The use of IVIG in SSc was first reported in the early 2000s, when three patients showed marked skin thickness reduction after a 6-monthly course of IVIG [11]. Subsequently, multiple studies have investigated the role of IVIG in SSc treatment, particularly in patients refractory to other immunomodulatory treatments [12-25]. The results of these studies show variable effect, as many are case series or observational studies with only one double blind randomised control trial (RCT) to date [12]. Whilst some studies have systematically examined the use of IVIG for a single organ system in SSc, none have comprehensively done so across multiple organ systems. Hence, this study aims to systematically review the available literature on the outcomes of IVIG in managing the various organ-specific manifestations of SSc.

Methods

A systematic literature search from the last 20 years (01/01/2003–15/04/2024) was conducted to identify studies regarding the use of IVIG in SSc in MEDLINE, EMBASE, Cochrane, Web of Science and Scopus. The search used both keywords and Medical Subject Heading (MeSH) terms related to SSc ("systemic sclerosis", "systemic scleroderma") and Intravenous Immunoglobulin ("IVIG"). The use of Boolean operators "AND", "OR" & "adj3" were used to ensure a comprehensive search was achieved. The search was limited to English language reports in adult humans (≥18 years of age). The reference lists of identified works were then hand-searched to find additional relevant articles. Two reviewers (SK & ZB) independently screened the titles and abstracts for potential relevance, and in the case of a conflict, consulted a third author (SO).

Inclusion/exclusion criteria

Following abstract review, a full text review and data extraction was conducted by a single author (SK) with additional inclusion criteria: studies in which ≥5 patients with SSc received IVIG, and those in which a measurable outcome was documented. Conference abstracts and other grey literature were excluded.

Population

Patients ≥18 years old with a diagnosis of SSc according to The European League Against Rheumatism and the American College of Rheumatology (ACR/EULAR) classification criteria [26].

Intervention

Treatment with at least once cycle of intravenous immunoglobulin.

Comparison

The presence of a control group was not required for inclusion.

Outcome

The primary outcome measured was the quantitative effect of IVIG treatment on an organ-specific manifestation of SSc. All studies collected data pre and post IVIG treatment to determine whether IVIG demonstrated a significant effect. Adverse effects were also collated as a secondary outcome.

Risk of bias

Assessment of the risk of bias for included RCTs was conducted according to the 2019 Cochrane Risk-of-Bias tool [27]. All other studies were assessed using the ROBINS-I "Risk-of-Bias in Non-randomised studies of intervention" tool [28]. The risk of bias assessment was conducted by one author (SK) and then subsequently reviewed by a second author (ZB).

Results

Study and subject characteristics

The search strategy identified 1482 studies; 1064 were removed as duplicates, leaving 418 potentially relevant studies. After initial abstract screening, a further 392 studies were excluded based on being preclinical, having <5 participants with SSc who received IVIG, no measurable outcome documented or with no full-text available (Fig. 1). There were no additional studies added through handsearching reference lists. Of the 26 studies retrieved, 12 were included in this review, comprising 354 patients (76 % with dcSSc, 23 % with lcSSc and 1 % with sine scleroderma) across one randomised control trial (RCT), two pilot studies, one open label study, seven retrospective studies and one case-control study (Table 1). Most patients were female (83 %), with an average age of 53.4 years at time of IVIG initiation (one study used age at SSc diagnosis rather than at treatment initiation so was excluded from the calculation of average age [15]). 31.6 % of patients across six studies had overlap SSc syndromes, most commonly myositis.

IVIG dosing and adverse effects

Of the twelve studies included, only three used a control group [12,14,15]; two compared IVIG to placebo [12,15], the other IVIG to relaxin, d-penicillamine, collagen and MMF [14]. The dose of IVIG used in the majority of studies (11/12) was 2 g/kg/month, distributed over 2–5 days, however one study employed a lower dose of 0.4 g/kg/month[21]. The number of cycles of IVIG varied greatly from a single dose [12,22,24] to up to 90 cycles [17]. Six studies used IVIG with concomitant immunosuppressants including cyclophosphamide, corticosteroids, azathioprine, methotrexate, MMF and hydroxychloroquine [7,14,15,17,21,25].

Seven studies reported adverse effects associated with IVIG use, the majority of which were minor, such as nausea, headache, or fever, and did not result in study withdrawal [7,12,14,15,20,22,25]. In total ten patients withdrew from studies, two due to acute kidney injury [14,15], two due to systemic hypertension [25] and one each due to haemolytic anaemia [25], thrombocytopenia [25], aseptic meningitis [14], transient ischaemic attack (TIA) [14], deep vein thrombosis (DVT) [7] and a dermatological reaction [7]. One study reported a death due to pre-existing cardiac disease [14]. Of note, one study observed that the

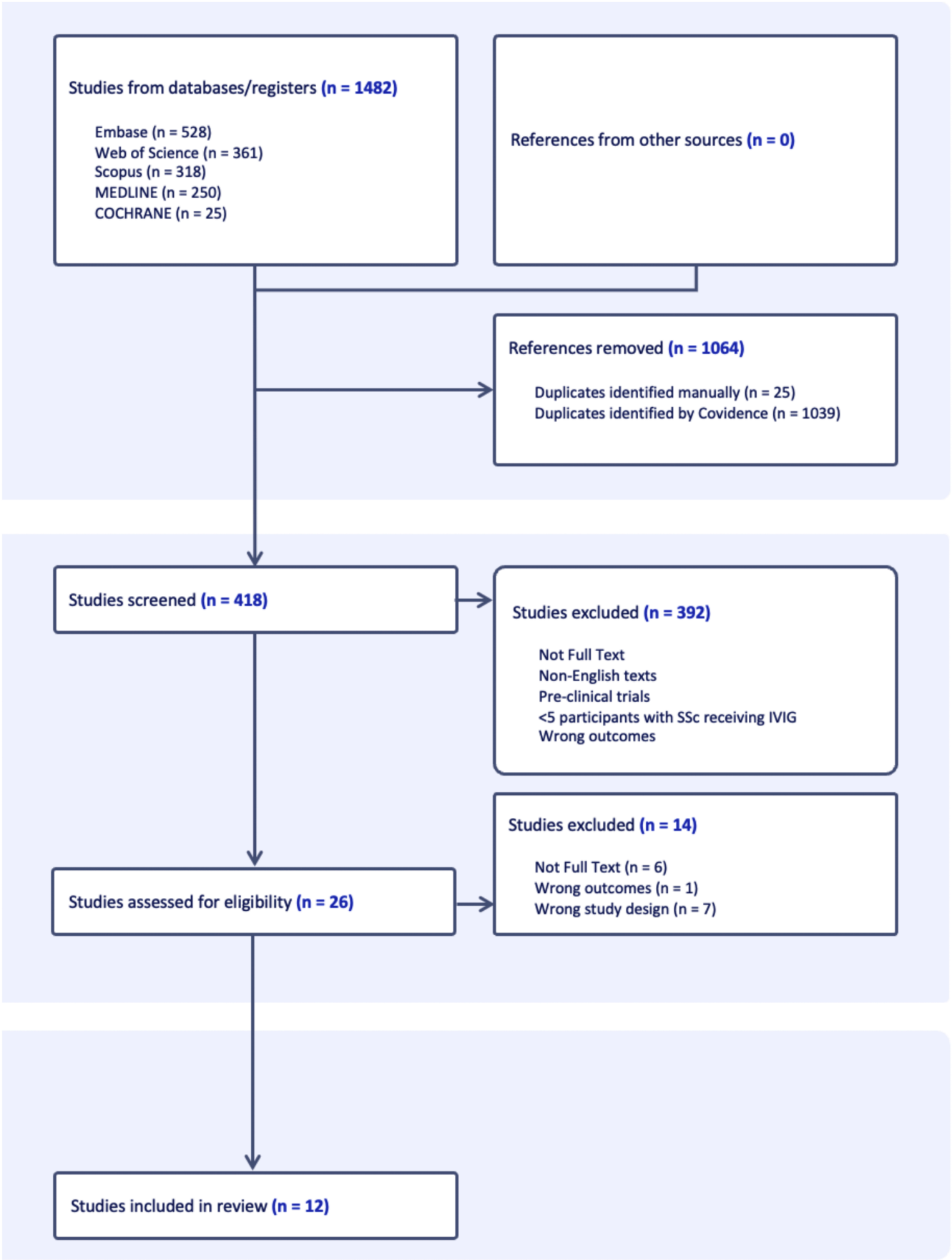

Fig. 1. PRISMA diagram outlining the search strategy and selection of studies.

Table 1
Summary of included studies and the SSc-specific reported outcomes.

Study	Design	Skin	Lung	MSK	GIT	Other
Takehara et al. [12]	Double Blind RCT	X	X			X
Nacci et al. [19]	Pilot Study	X		X		X
Matsuda et al. [24]	Pilot Study			X		
Levy et al. [16]	Open Label Study	X				X
Tandaipan et al. [25]	Retrospective Study	X	X	X	X	
Agostini et al. [20]	Retrospective Study	X	X			
Perkovic et al. [21]	Retrospective Study	X	X			
Chaigne et al. [15]	Retrospective Study	X	X			X
Poelman et al. [14]	Retrospective Study	X	X	X		X
Sanges et al. [7]	Retrospective Study	X	X	X	X	X
Raja et al. [17]	Retrospective Study	X	X	X	X	X
Ihn et al. [22]	Case Control	X				

GIT: gastrointestinal, MSK: musculoskeletal, RCT: randomised controlled trial.

patients receiving concomitant immunosuppressants had significantly more adverse events than those who received IVIG monotherapy, with 8/10 patients who experienced adverse events on dual therapy (p = 0.042) [25].

Study quality

Eleven of the included studies had a serious risk of bias in at least one domain of the ROBINS-I tool, meaning their overall risk was deemed serious. The ROBINS-I tool addresses bias across seven domains; confounding, participation selection, classification of intervention, deviation from intervention, missing data, outcome measurement and selection of reported result [28]. The most serious risk of bias stemmed from confounding and participant selection, as most studies were of small scale, administered concurrent immunosuppressants, and lacked a control group. The only RCT included was deemed as having an overall moderate risk of bias as per the Cochrane risk of bias tool ***(Supplementary Table 1)***.

Study outcomes

In total, 18 outcomes were documented, which were then grouped into five different outcome categories corresponding to a major SSc organ manifestation (Tables 2-6) – skin, respiratory, musculoskeletal, gastrointestinal, and other, which focused on patient and physician reported clinical improvement, in addition to corticosteroid-sparing benefit.

Skin

Eleven studies (n = 344) examined the effects of IVIG on SSc skin manifestations, demonstrated through four different outcomes (Table 2). All recorded the Modified Rodnan Skin Score (mRSS) as a measure of the extent of skin thickening, four measured a change in the presence of digital ulcers (DU), and one measured dermal fibrotic thickness (DFT).

With regards to the mRSS, 8/11 studies reported a significant improvement in scores after IVIG treatment [14,16,17,19-22,25]. In the study by Takehara et al. [12], participants were randomly allocated to receive either a dose of IVIG (n = 31) or placebo (n = 31) for 5 consecutive days, and the mRSS was then measured monthly over a 12 week period. Subjects who achieved at least a five point improvement in mRSS were then allocated to a long-term observational study, whilst those with less than a five point improvement were allocated to a re-administration study in which a single dose of IVIG was administered to all, regardless of whether they originally received IVIG or placebo. This created a scenario in which changes in mRSS were compared between those who received a single dose of placebo and then observed, a single dose of IVIG and then observed, a dose of placebo followed by a dose of IVIG in the re-administration study, and two doses of IVIG both originally and in the re-administration study. There was no significant difference in mRSS noted between patients who received a single dose of IVIG compared to those who received placebo at 12 weeks (mean change in mRSS −3.3±SD4.2 vs −4.2 ± 4.6, respectively, p-value unavailable). However in patients who were non-responders and enroled in the re-administration trial, there was a significant long term difference in mRSS between those who received two doses of IVIG compared to those who received placebo followed by IVIG (at 60 weeks, the least square difference minus mean mRSS was −8.3 ± 1.0 and −4.1 ± 1.1 respectively, p = 0.004).

Another study (n = 30) examined the effect of IVIG on the mRSS, and compared this with internal mRSS results of those treated with MMF, in addition to external results from three large RCTs that explored the effect of relaxin, d-pencillamine and bovine collagen on the mRSS [14]. The study noted a significant improvement in mRSS at 6, 12, 18 and 24 months post IVIG treatment, however compared to historical controls, the improvement in mRSS in the IVIG group at 6 months (−5.3 ± 7.9) was not statistically different to that of relaxin (−4.8 ± 7.0, p = 0.74) or MMF (−3.4 ± 7.4, p = 0.26) [14]. At 12 months however, the mean improvement in mRSS in the IVIG group (−8 ± 8.3) was significantly better than that of the d-penicillamine (−2.5 ± 8.6, p = 0.005) and collagen groups (−3.4 ± 7.1, p = 0.005), and comparable to the MMF group (−7.1 ± 9.0, p = 0.57) [14]. It is important to note that the baseline characteristics of the patients treated with IVIG differed to those in the historical controls, with more severe skin disease noted at baseline in the IVIG patients compared to those in the d-penicillamine and collagen studies [14]. Regarding DFT, one study (n = 63) found a mean decrease by 2.23 % (±34.38) in the IVIG group, compared to a mean increase by 7.51 % (± 25.55) in the placebo group, however they noted that this was not statistically significant (p-value not stated) [12].

Some benefit of IVIG for DUs was seen in four studies, with one study (n = 9) reporting healing in all six patients with DU after 1–5 cycles of IVIG [21] and another (n = 5) citing incidental healing in one patient [22]. The third study noted no new DUs emerging in 4/7 patients during treatment [17], however all seven patients were on oral vasodilators and five were on prostacyclin infusions. The last study (n = 46) reported a reduction in the number of patients with active DU from 6 pre-IVIG to 4 at follow-up (p = 0.72), as well as a decrease in the mean number of active DU reported by each patient from 0.52 (±1.3) pre-IVIG to 0.15 (±0.4) at follow up (p = 0.19) [7], with neither outcome reaching statistical significance.

Respiratory

Seven studies (n = 293) recorded the effects of IVIG on respiratory function, reflected through four different outcomes (Table 3): pulmonary function tests (PFTs), 6-minute-walk test (6MWT), changes on chest computed tomography (CT) and New York Heart Association (NYHA) score [7,12,14,15,17,21,25]. All studies examined PFTs, including forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO).

No studies observed a statistically significant improvement in FVC, however results did remain stable; one study (n = 30) reported an FVC of 83 % (±19.6) at baseline compared to 83.8 % (±16.8) after 12 months (p = 0.678) [14], the next (n = 78) cited a mean FVC of 77.8 % (±24.7) at baseline compared to 78.1 % (±23.4) after 9 cycles of IVIG (p = 0.346) [25], another (n = 46) noted a change from 73.3 % (±18.7) to 75.1 % (±18.9) after 12 months (p = 0.91) [7], and the fourth (n = 52) reported

Table 2
Summary of studies reporting the effect of IVIG on cutaneous manifestations of SSc.

Study	Design	Country	Population	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	MRSS	DU	DFT
Takehara et al. [12]	Double Blind RCT	Japan	63 dSSc	2 g/kg/ 5 days/ at month 0 +/- 2 g/kg/5 days/at month 6	1–2 cycles	18 months	31 received IVIG, 32 received placebo	Nil	10/31 of IVIG reported AE vs 4/32 of placebo. Main AE were elevated CRP & ALT.	No sig difference between MRSS scores in IVIG (−3.3 ± 4.2) vs placebo (−4.2 ± 4.6) at 6 weeks. Sig difference in MRSS in IVIG (−8.3 ± 1.0) vs placebo (−4.1 ± 1.1) after readmission study, 60wk after original dose ($p = 0.004$).		Mean improvement in thickness by −2.23 % ± 34.48 in IVIG vs 7.51 % ± 25.55 in placebo at 6wk. Not sig.
Nacci et al. [19]	Pilot	Italy	7 (5 lSSc, 2 dSSc) Refractory to MTX & CYC	2 g/kg/ 4 days/ month	6 cycles	6 months	None	Nil	Nil reported.	Sig improvement in mean MRSS from 29.2 (SD=3.9) to 21.1 (SD=4.6), $p = 0.003$.		
Levy et al. [16]	Open Label	Italy, Israel	15 (5 lSSc, 10 dSSc)	2 g/kg/ 5 days/ month	3–6 cycles	6 months	Nil	Nil	Nil reported	Mean sig improvement in MRSS of -10 ± 5.9 ($p < 0.001$), with an estimated 25 % decrease in skin involvement. Shorter disease duration <2years showed a 21 % improvement in MRSS vs a 44 % improvement in those with disease duration >2 years ($p = 0.053$).		
Tandaipan et al. [25]	Retrospective Study	Spain	78 (50 % overlap with other CTD, most commonly IIM in 41 %	2 g/kg/ 5 days/ month	Median 5 cycles (1–60)	17 months	Nil	69 % glucocorticoids, 10 % MTX, 5 %CYC, 15 % AZA, 37 % MMF, 18 % biologics	12 AE in 10 patients: 3x systemic hypertension, haemolytic anaemia, thrombocytopenia, haemorrhage, 3x headache, dystrophy, 2x oral candidiasis. 4x patients withdrew.	MRSS decreased from 15± 12.4to 13±12.5 after mean 7 cycles of IVIG. $P = 0.015$		
Agostini et al. [20]	Retrospective Study	Italy	24 dSSc	2 g/kg/ 4 days/ month	12 cycles	12 months	Nil	Nil	Minor AEs reported e.g. hypotension, nausea, dizziness	Sig improvement of −6.61 ± 5.2 ($p < 0.0001$) at 6 months and a further sig improvement of −5.05 ± 4.88 ($p < 0.0002$) at 12 months.		
Chaigne et al. [15]	Retrospective Study	France	52 (18 lSSc, 34 dSSc)	2 g/kg/ 2–3 days/	Median 6 cycles (IQR 2–16)	Median 79 months,	18 received IVIG, 34 received placebo	7 received CS, 1 only IVIG, 5 CS & MTX, 1 received CS & AZA, 1 received CS & AZA &	44 % had AE - 2 patients had AKI with known CKD and 1 had aseptic mentingitis. Only AKI	No sig difference in change in MRSS between IVIG and placebo (0 vs		

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Table 2 (*continued*)

Study	Design	Country	Population	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	MRSS	DU	DFT
				1–2 months		(IQR 43–147)		MTX, 1 received MTX, 1 received AZA, 1 received MMF	patients discontinued therapy.	0 respectively, $p = 0.035$)		
Poelman et al. [14]	Retrospective Study	USA	30 dSSc (5/30 with myositis-overlap)	2 g/kg/3–5 days/month	3–24 cycles	24 months	Historical controls of 3 multicentre RCT (relaxin, D-pen collagen & MMF)	70 % MMF, 33.3 % CS, 20 % CYC, 10 % MTX, 3.3& imatinib, 3.3 % HCQ	Headache 40 %, fatigue 23.3 %, nausea 13.3 %, fever 10 %, myalgia 10 %, rash 10 %. 1 discontinued due to aspetic meningitis, 1 discontinued due to TIA, 1 died of cardiac arrest due to pre-existing cardiomyopathy	Sig mean improvement at 6 months from 29.6 ± 7.2 to 24.1 ± 9.6 ($p = 0.0011$). Sig further mean improvement at 12 months to 22.5 ± 10.0 ($p = 0.0001$), and to 20.6 ± 11.8 ($p = 0.0001$) at 18 months, and then 15.3 ± 6.4 ($p < 0.0001$) at 24 months. The mean change in mRSS at 6 months was not sig different in the IVIG group (− 5.3 ± 7.9) compared to the Relaxin (− 4.8 ± 6.99, $p = 0.74$) or MMF group (− 3.4 ± 7.4, $p = 0.26$). At 12 months the mean change in mRSS was sig better in the IVIG group (− 8 ± 8.3) than in the D-penacillamine (− 2.47 ± 8.6, $p = 0.005$) and Collagen (− 3.4 ± 7.12, $p = 0.005$) groups and similar to MMF (− 7.1 ± 9, $p = 0.67$)		
Perkovic et al. [21]	Retrospective Study	Croatia	9 (8 dSSc, 1 1 lSSc)	0.4 g/kg/2 days/month	3–13 cycles	13 months	Nil	100 % also had IV CYC 600 mg/m^2 given on second day of IVIG infusion	Nil reported	Improvement in MRSS in 3 of 4 patients (−5, −2, −9, +2)	Healing of DU in 6/6 patients. Time of healing occurred within 1–5 cycles of IVIG.	
Sanges et al. [7]	Retrospective Study	France	46 (39/46 (85 %) overlap)	2 g/kg/2–4 days/month	Mean 14.5 cycles (SD 18.2)	Mean 14.8 months (SD 19.4)	Nil	87 % steroids, 11 % CYC, 30 % MTX, 13 % AZA, 26 % MMF, 4 % HCQ	3 cases of fever, 3 rashes, 3 headaches. 1 case of DVT & 1 case of diffuse oedematous syndrome, both resulting in cessation	No sig difference in MRSS pre-IVIG (17.6 ± 10.9) to post-IVIG (17.0 ± 12.6), $p = 0.57$.	Slight reduction in number of patients with active DU pre-IVIG (6) vs post IVIG (4). $P = 0.72$. Mean number of DU on these patients fell from 0.52 ± 1.3	

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Table 2 (*continued*)

Study	Design	Country	Population	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	MRSS	DU	DFT
											to 0.15 ± 0.4. *P* = 0.19.	
Raja et al. [17]	Retrospective Study	UK	15 SSc-myositis-overlap	2 g/kg/ 1–3 days/ 1–1.5 months	2–90 cycles	135 months	Nil	"...all received standard dose of immunsuppressive agents..."	Nil reported	Sig improvement in MRSS from 21.5 (SD=13.8) to 10 (SD=10.6), (p = 0.005)	4/7 patients reported no new DU during treatment. However all 7 were on oral vasodilators and 5 were on prostacyclin infusions.	
Ihn et al. [22]	Case Control	Japan	5 dSSc	2 g/kg/ 5 days/ month	1 cycle	16 months	Nil	Nil	1 headache, 1 nausea	Marked improvement in 5/5 patients ($p < 0.01$)	Incidental DU healing in 1 patient during trial	

AE: adverse effects, AKI: acute kidney injury, ALT: alanine transaminase, AZA: azathioprine, CKD: chronic kidney disease, CRP: C-reactive Protein, CS: corticosteroids, Cx: concomitant, CYC: cyclophosphamide, DFT: dermal fibrotic thickness, DU: digital ulcers, DVT: deep vein thrombosis, HCQ: hydroxychloroquine, IQR: interquartile ratio, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, MRSS: Modified Rodnan Skin Score, MTX: methotrexate, pt: patient, SD: standard deviation, Sig: significant, UK: United Kingdom, wk: week.

a 5 % improvement in IVIG group compared to a 1 % improvement in placebo ($p = 0.80$) [15]. Regarding TLC, one study ($n = 46$) reported stable results, with a TLC of 78.3 % (±16.8) pre-, compared to 74.7 % (±17.7) post IVIG ($p = 0.80$) [7], whilst the other ($n = 52$) recorded a 1 % improvement in the IVIG group compared to 2 % in placebo group [7,15]. With regards to DLCO, six studies recorded no significant change: five studies ($n = 232$) noted a stabilisation in DLCO values post IVIG treatment [7,12,14,17,25] and one ($n = 52$) reported a marginal decrease in DLCO of 15 % for IVIG compared to 4 % in placebo ($p = 0.331$) [15]. Only one study reported a significant improvement in DLCO in all three patients with improvements of 7 %, 10 % and 12 % from baseline post at least three cycles of IVIG, although this study administered concurrent cyclophosphamide [21].

Two studies reported conflicting changes in the 6MWT [7,21]. The first reported a significant improvement in the only patient to successfully complete the test, with four other patients also self-reporting less dyspnoea after IVIG treatment [21]. The other study however ($n = 46$) recorded a mean decrease in the distance walked from 414 m (±89) to 393 m (± 93) post IVIG treatment ($p = 0.40$) [7]. This same study also looked at changes on chest CT after IVIG, and noted that of the 27 patients with CT results, there was stabilisation in the number of those with ground glass opacities (11 pre-IVIG to 8 post IVIG, $p = 0.38$) and fibrotic lesions (remained at 11) after IVIG therapy [7]. It was not stated whether these specific patients were receiving concomitant immunosuppressants. This study also found no significant improvement in dyspnoea, as measured by a change in NYHA score post IVIG treatment ($p = 0.96$) [7].

Musculoskeletal

Five studies ($n = 176$) reported on the efficacy of IVIG on SSc musculoskeletal involvement as measured by joint involvement, joint pain, muscle pain, muscle weakness, serum creatinine kinase (CK) measurements and the presence of tendon friction rubs (TFR) (Table 4) [7,14,17,19,25].

Two studies ($n = 53$) reported changes in joint pain and joint involvement after IVIG. The first ($n = 7$) reported a significant improvement in joint involvement ($p < 0.001$), as measured by the Ritchie Index (RI) [29] from 25.6 (±6.7) to 21.1 (±4.6), and a significant improvement in joint pain ($p = 0.03$), measured by the Visual Analogue Scale (VAS) [30], from 4.7 (±1.9) to 0.7 (±1.7) [19]. The second study ($n = 46$) reported a marked improvement in joint pain ($p = 0.02$), with 44 % of patients experiencing pain pre-IVIG reduced to 19 % post IVIG [7]. This study was the only one to report on muscle pain with a significant reduction in the number of patients experiencing pain from 74 % to 20 % post treatment ($p = 0.0001$) [7]. Two studies ($n = 124$) reported on muscle weakness, whereby the number of patients with weakness was defined by those with at least one muscle group with a strength score <3/5 as per the Medical Research Council (MRC) muscle strength scale [31]. Both studies noted a significant improvement in weakness, with the first noting an improvement in 24 % of patients ($p = 0.01$) [7] and the second noting a benefit in 92 % of patients ($p = 0.00$). With regards to TFRs, a finding often associated with fibrin deposition in SSc [32], one study found resolution of TFRs in 7/10 patients [14].

Four studies measured CK levels: three ($n = 139$) reported a significant improvement in mean CK values of 1069 U/L (±1552) to 288 U/L (±449), 1149 U/L (±2046) to 217 U/L (±224) and median CK 192 U/L (IQR 36–3193) to 77 U/L (IQR 42–465) respectively after IVIG treatment ($p = 0.0001$, $p = 0.02$ and $p = 0.025$) [7,17,25]. The fourth noted "normalisation" in CK levels across all four patients with CK serology available ($p = 0.054$) [14]. It is important to note that the vast majority of patients in these studies had SSc-myositis overlap syndromes.

Gastrointestinal

Four studies ($n = 149$) examined the effects of IVIG on

Table 3
Summary of studies reporting the effect of IVIG on pulmonary manifestations of SSc.

Study	Design	Country	Population	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	PFT	6 min walk Test	Chest CT	NYHA
Takehara et al. [12]	Double Blind RCT	Japan	63 dSSc	2 g/kg/5 days/at month 0 +/- 2 g/kg/5 days/at month 6*	1–2 cycles	18 months	31 received IVIG, 32 received placebo	Nil	10/31 of IVIG had AE vs 4/32 of placebo. Main AE were elevated CRP & ALT.	No sig improvement in FVC or DLCO.			
Tandaipan et al. [25]	Retrospective Study	Spain	78 (50 % overlap with other CTD, most commonly IIM in 41 %	2 g/kg/5 days/month	Median 5 cycles (1–60)	17 months	Nil	69 % glucocorticoids, 10 % MTX, 5 %CYC, 15 % AZA, 37 % MMF, 18 % biologics	12 AE in 10 patients: 3x systemic hypertension, haemolytic anaemia, thrombocytopenia, haemorrhage, 3x headache, dystrophy, 2x oral candidiasis. 4x patients withdrew.	FVC decreased from 77.75 ±24.73 to 78.11±23.36 after mean 9 cycles IVIG. $P = 0.346$ DLCO decreased from 64.78±19.41 to 62.17 ±23.37 after mean 9 cycles IVIG. $P = 0.529$			
Perkovic et al. [21]	Retrospective Study	Croatia	9 (8 dSSc, 1 lSSc)	0.4 g/kg/2 days/month	3–13 cycles	13 months	Nil	100 % also had IV CYC 600 mg/m2 given on second day of IVIG infusion	Nil reported	Improvement in DLCO in 3/3 patients (+10 %, +12 %, +7 % from baseline)	Improvement in 1/1 patient. 4 patients report feeling less dyspnoeic.		
Chaigne et al. [15]	Retrospective Study	France	52 (18 lSSc, 34 dSSc)	2 g/kg/2–3 days/1–2 months	Median 6 cycles (IQR 2–16)	Median 79 months (IQR 43–147)	18 received IVIG, 34 received placebo	7 received CS, 1 only IVIG, 5 CS & MTX, 1 received CS & AZA, 1 received CS & AZA & MTX, 1 received MTX, 1 received AZA, 1 received MMF	44 % had AE - 2 patients had AKI with known CKD and 1 had aseptic mentingitis. Only AKI patients discontinued therapy.	No sig difference in median change in FVC between IVIG (5 %) vs placebo (1 %), $p = 0.80$. No sig difference in median change in TLC between IVIG (1 %) vs placebo (2 %), $p = 0.49$. No sig difference in median change in DLCO between IVIG (−15 %) vs placebo (−4 %), $p = 0.46$.			

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Table 3 (*continued*)

Study	Design	Country	Population	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	PFT	6 min walk Test	Chest CT	NYHA
Poelman et al. [14]	Retrospective Study	USA	30 dSSc (5/30 myositsi-overlap)	2 g/kg/3–5 days/month	3–24 cycles	24 months	Historical controls of 3 multicentre RCT (relaxin, D-pen, collagen & MMF)	70 % MMF, 33.3 % prednisone, 20 % CYC, 10 % MTX, 3.3& imatinib, 3.3 % HCQ	Headache 40 %, fatigue 23.3 %, nausea 13.3 %, fever 10 %, myalgia 10 %, rash 10 %. 1 discontinued due to aspetic meningitis, 1 due to TIA, 1 died of cardiac arrest due to pre-existing cardiomyopathy	FVC at baseline was 83 % (SD=19.6) vs 83.8 % (SD=16.8) at 12 months. No sig improvement $p = 0.678$. DLCO at baseline was 76.3 % (SD=21) vs 79.9 % (SD=23.1) at 12 months. No sig improvement $p = 0.331$.			
Sanges et al. [7]	Retrospective Study	France	46 (85 % overlap)	2 g/kg/2–4 days/month	Mean 14.5 cycles (SD 18.2)	Mean 14.8 months (SD19.4)	Nil	87 % steroids, 11 % CYC, 30 % MTX, 13 % AZA, 26 % MMF, 4 % HCQ	3 cases of fever, 3 rashes, 3 headaches. 1 case of DVT & 1 case of diffuse oedematous syndrome, both resulting in cessation	No sig improvement in FVC (73.3 % +/−18.7 to 75.1 % +/- 18.9, $p = 0.91$), TLC (78.3 % +/- 16.8 to 74.7 +/- 17.7, $p = 0.80$) or DLCO (50.2 +/- 22.9 to 53.8 +/- 23.2, $p = 0.30$)	No sig change from 414 *m* +/−89 to 393 *m* +/- 93. $P = 0.40$.	No sig change in number of patients with ground glass opacities (11 to 8 post IVIG, $p = 0.38$) or number with fibrotic lesions (remained at 11)	No sig improvement (1.71 +/−0.8 to 1.68 +/- 0.8, $p = 0.96$) post IVIG.
Raja et al. [17]	Retrospective Study	UK	15 myositis-overlap	2 g/kg/1–3 days/1–1.5 months	2–90 cycles**	135 months	Nil	"all received standard dose of immunosuppressive agents"	Nil reported	No sig improvement in FVC or DLCO.			

* Takehara et al. gave subjects either a single dose of IVIG or placebo at week 0, and measured their MRSS. 12 weeks later they re-measured MRSS and subjects who had >5 point improvement in MRSS were subjected to long-term observational study whilst those with less than a 5 point improvement were subjected to a readministration study in which another single course of IVIG was administered in a further 12 weeks (24 weeks after the original dose).

** Raja et al. retrospectively recruited subjects who received IVIG ranging at an interval of 6 weeks – 4 months for a mean duration of 2.3 years, range 3 months - 135 months. Therefore the range in number of cycles of IVIG has been calculated as a minimum of 2 (6 week cycles over a 3 month period) and a maximum of 90 (6 weekly cycles over 135 months), however if the patients at the extremes were receiving 4 monthly intervals between treatments, the number of cycles will be fewer.

6MWT: 6 min walk test, AE: adverse effects, AKI: acute kidney injury, ALT: alanine transaminase, AZA: azathioprine, CKD: chronic kidney disease, CRP: C-reactive Protein, CS: corticosteroids,

CT: computed tomography, Cx: concomitant, CYC: cyclophosphamide, DLCO: diffusion capacity of carbon monoxide, DVT: deep vein thrombosis, FVC: forced vital capacity, HCQ: hydroxychloroquine, IVIG: intravenous immunoglobulin, MTX: methotrexate, MMF: mycophenolate mofetil, NYHA: New York Health Association score, PFT: pulmonary function tests, pt: patient, Sig: significant, TLC: total lung capacity, wk: week.

Table 4
Summary of studies reporting the effect of IVIG on musculoskeletal manifestations of SSc.

Study	Design	Country	Population	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	Joint Involvement (RI)	Joint Pain	TFR	Serial CK (U/L)	Muscle Pain	Muscle Weakness (MRC)
Nacci et al. [19]	Pilot	Italy	7 (5 lSSc, 2 dSSc)	2 g/kg/ 4 days/ month	6 cycles	6 months	None	Nil. Pt were refractory to MTX & CYC pulse therapy	Nil reported.	Mean improvement from 25.6 (SD=6.7) to 21.1 (SD=4.6). $p <$ 0.001.	Sig mean improvement in VAS from 4.7 (SD=1.9) to 0.7 (SD=1.7), $p =$ 0.03.				
Tandaipan et al. [25]	Retrospective Study	Spain	78 (50 % overlap with other CTD, most commonly IIM in 41 %	2 g/kg/ 5 days/ month	Median 5 cycles (1–60)	17 months	Nil	69 % glucocorticoids, 10 % MTX, 5 %CYC, 15 % AZA, 37 % MMF, 18 % biologics	12 AE in 10 patients: 3x systemic hypertension, haemolytic anaemia, thrombocytopenia, haemorrhage, 3x headache, dystrophy, 2x oral candidiasis. 4x patients withdrew.				CK decreased from 1149 ±2046 UI/mL to 217±224 UI/mL after mean 9 cycles of IVIG. $P =$ 0.02		Number of pt with MRC <3/5 decreased from 26 to 2 after IVIG. P = 0
Poelman et al. [14]	Retrospective Study	USA	30 dSSc (5/ 30 myositis-overlap)	2 g/kg/ 3–5 days/ month	3–24 cycles	24 months	historical controls of 3 multicentre RCT (relaxin, D-penacillamine collagen & MMF)	70 % MMF, 33.3 % prednisone, 20 % CYC, 10 % MTX, 3.3& imatinib, 3.3 % HCQ	Headache 40 %, fatigue 23.3 %, nausea 13.3 %, fever 10 %, myalgia 10 %, rash 10 %. 1 discontinued due to aspetic meningitis, 1 discontinued due to TIA, 1 died of cardiac arrest due to pre-existing cardiomyopathy			Resolution in 7/10 patients. Ongoing TFR in 2/ 10 and 1 patient was lost to follow up.	Normalisation in 4/4 patients with concomitant myositis ($p =$ 0.054)		
Sanges et al. [7]	Retrospective Study	France	46 (85 % overlap)	2 g/kg/ 2–4 days/ month	Mean 14.5 cycles (SD 18.2)	Mean 14.8 months (SD19.4)	Nil	87 % steroids, 11 % CYC, 30 % MTX, 13 % AZA, 26 % MMF, 4 % HCQ	3 cases of fever, 3 rashes, 3 headaches. 1 case of DVT & 1 case of diffuse oedematous syndrome, both resulting in cessation		Sig improvement from 44 % patients to 19 % of patients ($p = 0.02$)		Sig improvement from 1069 ± 1552 to 288 ± 449 ($p =$ 0.0001)	Sig improvement from 74 % patients to 20 % patients ($p = 0.0001$)	Number of pt with MRC <3/5 decreased from 17 to 8 after IVIG. $P =$ 0.01
Raja et al. [17]	Retrospective Study	UK	15 myositis-overlap	2 g/kg/ 1–3 days/ 1–1.5 months	2–90 cycles	135 months	Nil	"all received standard dose of immunsuppressive agents"	Nil reported				Sig median improvement from 192 (35–3192) to 77 (42–465, ($p =$ 0.025).		

AE: adverse effects, AKI: acute kidney injury, AZA: azathioprine, CK: creatinine kinase, Cx: concomitant, CS: corticosteroids, CYC: cyclophosphamide, DVT: deep vein thrombosis, HCQ: hydroxychloroquine, IVIG: intravenous immunoglobulin, MTX: methotrexate, MMF: mycophenolate mofetil, MRC: Medical Research Council scale for muscle strength, pt: patient, RI: Ritchie index, Sig: significant, TFR: Tendon Friction Rubs, VAS: visual analogue pain scale, wk: week.

Table 5
Summary of studies reporting the effect of IVIG on gastrointestinal manifestations of SSc.

Study	Design	Country	Pop	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	Upper GI Sx (RDQ)	Lower GI Sx (GIT2.0)
Matsuda et al. (2023)	Pilot Study	Japan	10 (all myositis overlap)	2 g/kg/5 days	1 cycle	1 week	Nil	Nil	Nil reported		Reduction in total GIT scores with statistical significance, as well as individually in most subscales. Figure & P value not available.
Sanges et al. [7]	Retrospective Study	France	46 (85 % overlap)	2 g/kg/ 2–4 days/ month	Mean 14.5 cycles (SD 18.2)	Mean 14.8 months (SD19.4)	Nil	87 % steroids, 11 % CYC, 30 % MTX, 13 % AZA, 26 % MMF, 4 % HCQ	3 cases of fever, 3 rashes, 3 headaches. 1 case of DVT & 1 case of diffuse oedematous syndrome, both resulting in cessation	Improvement from 68 % to 53 % patients ($p = 0.06$), but not sig	Improvement from 42 % to 27 % of patients ($p = 0.06$), but not sig
Raja et al. [17]	Retrospective Study	UK	15 (all overlap myositis patients)	2 g/kg/ 1–3 days/ 1–1.5 months	2–90 cycles	135 months	Nil	"all received standard dose of immunosuppressive agents"	Nil reported	sig improvement in GORD frequency from 3.19 (SD=1.79) to 1.88 (SD=0.90) post IVIG, $p = 0.006$. sig improvement in GORD intensity from 3.03 (SD=1.70) to 1.96 (SD=0.86) post IVIG, $p = 0.013$.	sig improvement from 1.07 (SD=0.67) to 0.60 (SD=0.46) post IVIG, ($p = 0.002$)
Tandaipan et al. [25]	Retrospective Study	Spain	78 (50 % overlap with other CTD, most commonly IIM in 41 %	2 g/kg/5 days/ month	Median 5 cycles (1–60)	17 months	Nil	69 % glucocorticoids, 10 % MTX, 5 %CYC, 15 % AZA, 37 % MMF, 18 % biologics	12 AE in 10 patients: 3x systemic hypertension, haemolytic anaemia, thrombocytopenia, haemorrhage, 3x headache, dystrophy, 2x oral candidiasis. 4x patients withdrew.		GIT score decreased from 1.06±0.61 to 0.78 ±0.4 after mean 3x cycles of IVIG. $P = 0.05$

AZA: azathioprine, CYC: cyclophosphamide, Cx: concomitant, DVT: deep vein thrombosis, GI: gastrointestinal, GORD: gastroesophageal reflux disease, GIT2.0: lower gastrointestinal tract disease questionnaire, HCQ: hydroxychloroquine, IVIG: intravenous immunoglobulin, MTX: methotrexate, MMF: mycophenolate mofetil, RDQ: reflux disease questionnaire, Sig: significant.

Table 6
Summary of studies reporting the effect of IVIG on clinical improvement and steroid sparing benefit.

Study	Design	Country	Pop	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	Function (HAQ/ HAQ-DI)	Clinical improvement	Corticosteroid Sparing
Takehara et al. (2013)	Double Blind RCT	Japan	63 (diffuse SSc)	2 g/kg/5 days/at month 0 +/- 2 g/kg/5 days/at month 6	1–2 cycles	18 months	31 given IVIG, 32 given placebo	Nil	10/31 of IVIG had AE vs 4/32 of placebo. Main AE were elevated CRP & ALT.	No sig improvement in HAQ		
Nacci et al. [19]	Pilot	Italy	7 (5 limited SSc, 2 diffuse SSc)	2 g/kg/4 days/ month	6 cycles	6 months	None	Nil. Pt were refractory to MTX & CYC pulse therapy	Nil reported.	Sig mean improvement in HAQ from 2.3 (SD=0.9) to 1 (SD=0.8), p = 0.03. Improvement in 6/7 patients.		
Levy et al. [16]	Open Label	Italy/ Israel	15 (5 limited, 10 diffuse)	2 g/kg/5 days/ month	3–6 cycles	6 months	Nil	Nil	Nil reported	Mean improvement in HAQ from 2.7 to 1.3 (p = 0.03)		
Chaigne et al. [15]	Retrospective Study	France	52 (18 limited, 34 diffuse)	2 g/kg/ 2–3 days/ 1–2 months	6 cycles (median), IQR 2–16	79 months (median), IQR 43–147	18 given IVIG, 34 given placebo	7 received CS, 1 only IVIG, 5 CS & MTX, 1 received CS & AZA, 1 received CS & AZA & MTX, 1 received MTX, 1 received AZA, 1 received MMF	44 % had AE - 2 patients had AKI with known CKD and 1 had aseptic mentingitis. Only AKI patients discontinued therapy.		Remission obtained in 18/ 18 of IVIG vs 28/ 34 on placebo (p = 0.55) Median time to relapse in IVIG was 23 (3.8–52) months vs 12 (4.3–99.8) months for placebo. This was not sig different, p = 0.97)	1 year post treatment, median CS dose 13.0 sig at $p <$ 0.05.
Poelman et al. [14]	Retrospective Study	USA	30 (diffuse SSc) - 5 with concomitant myositis	2 g/kg/ 3–5 days/ month	3–24 cycles	24 months	historical controls of 3 multicentre RCT uing relaxin, D-pen collagen & MMF	70 % MMF, 33.3 % prednisone, 20 % CYC, 10 % MTX, 3.3& imatinib, 3.3 % HCQ	Headache 40 %, fatigue 23.3 %, nausea 13.3 %, fever 10 %, myalgia 10 %, rash 10 %. 1 discotinued due to aspetic meningitis, 1 discontinued due to TIA, 1 died of cardiac arrest due to pre-existing cardiomyopathy	Mean improvement in HAQ-DI from 1.29 (SD=0.70) to 1.21 (SD=0.72) after 12 months. Not sig (p = 0.436)	sig improvement in patient-reported disease activity from 1.63 (SD=0.72) to 1.07 (SD=0.76) after 12 months, p = 0.001. Physician assessment of disease activity was that 18/30 patients improved & 4/30 stabilised.	
Sanges et al. [7]	Retrospective Study	France	46 (85 % overlap)	2 g/kg/ 2–4 days/ month	14.5 cycles (mean) +/- 18.2 SD	14.8 months (mean) +/- 19.4 (SD)	Nil	87 % steroids, 11 % CYC, 30 % MTX, 13 % AZA, 26 % MMF, 4 % HCQ	3 cases of fever, 3 rashes, 3 headaches. 1 case of DVT & 1 case of diffuse oedematous			Sig improvement from 13.0 +/−11.6 mg/day to 8.9+/- 10.4

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Table 6 (*continued*)

Study	Design	Country	Pop	IVIG dose	IVIG duration	Study duration	Comparator	Cx Therapy	Adverse Effects	Function (HAQ/ HAQ-DI)	Clinical improvement	Corticosteroid Sparing
									syndrome, both resulting in cessation			mg/day (p = 0.01)
Raja et al. [17]	Retrospective Study	UK	15 (all overlap myositis patients)	2 g/kg/ 1–3 days/ 1–1.5 months	2–90 cycles	135 months	Nil	"all received standard dose of immunsuppressive agents"	Nil reported			median steroid dose reduction of 8.75 (2.5–17.5) mg/day. CS sparing effect occurred in 8/13 patients.

AE: adverse effects, AKI: acute kidney injury, ALT: alanine transaminase, AZA: azathioprine, CRP: C-reactive Protein, CS: corticosteroids, Cx: concomitant, CYC: cyclophosphamide, DVT: deep vein thrombosis, HAQ: health assessment questionnaire, HCQ: hydroxychloroquine, IVIG: intravenous immunoglobulin, MTX: methotrexate, MMF: mycophenolate mofetil, pt: patient, Sig: significant, wk: week.

gastrointestinal (GI) manifestations of SSc [7,17,24,25], reflected through changes in gastroesophageal reflux disease (GORD) symptoms, measured by the Reflux Disease Questionnaire (RDQ) [33], and lower GI symptoms, reported through the University California Los Angeles Scleroderma Clinical Trial Consortium (UCLA) gastrointestinal tract questionnaire (GIT2.0) (Table 5) [34].

One study (n = 15) reported a significant improvement in GORD frequency (p = 0.006) and intensity (p = 0.013) post IVIG treatment [17], whilst another (n = 46) reported a near significant improvement in the number of patients experiencing GORD symptoms from 68 % to 53 % (p = 0.06) [7]. This same trend was reflected in these studies with regards to the UCLA GIT2.0 score, with the first study (n = 15) reporting a significant improvement from 1.07 (±0.67) to 0.60 (±0.46) post IVIG (p = 0.002) [17], and the second (n = 46) reporting 15 % fewer patients with abnormal bowel symptoms post treatment (p = 0.06) [7]. A third study noted a significant improvement in the GIT score from 1.06 (±0.61) to 0.78 (±0.4) after an average of 3 IVIG cycles (p = 0.05) [25] whilst the fourth study administered only a single dose of IVIG, however still observed a statistically significant reduction in the overall GIT score as well as in the reflux, bloating, social functioning and emotional wellbeing subsets of the score (exact figures and p value unavailable) [24]. Notably, the first three of these studies administered concomitant therapy alongside IVIG [7,17,24,25] whilst the final study slightly adapted the UCLA GIT2.0 score into a more culturally appropriate Japanese version [24].

Other

Five studies (n = 167) recorded the effects of IVIG on inducing patient or physician-reported clinical improvement (Table 6) [12,14-16,19]. Four studies (n = 115) evaluated patient-reported functional status using the Health Assessment Questionnaire (HAQ), which assesses five health domains to encapsulate the long-term impact of chronic illness. Part of the HAQ is the HAQ disability index (HAQ-DI), which assesses the degree of disability experienced by patients in eight life domains secondary to their medical condition [35]. Two studies reported a marked mean improvement in overall HAQ; the first (n = 15) from 2.7 to 1.3 (p = 0.03) [16] and the second (n = 7) from 2.3 (±0.9) to 1.0 (±0.8), with benefits experienced in 6/7 patients (p = 0.03) [19]. The third study (n = 30) only examined HAQ-DI, and although they recorded a slight improvement in the HAQ-DI score from 1.29 (±0.70) to 1.21 (±0.72), the change was not significant (p = 0.436) [14]. The last study (n = 63) reported no improvement in HAQ [12]. There were no joint or muscle specific outcomes listed amongst the findings of the HAQ.

In addition to patient-reported measures, two studies (n = 82) also noted physician-reported clinical improvement and time to relapse [14,15]. One study (n = 52) on SSc associated myopathy documented that 100 % of the IVIG cohort achieved remission compared to 82 % of placebo patients (p = 0.55), and the median time to myopathy relapse was 23 months (IQR 3.8–52), compared to 12 months (IQR 4.3–99.8) in the placebo cohort (p = 0.97) [15].

Finally, three studies (n = 113) examined a potential corticosteroid sparing effect of IVIG [7,15,17]. All reported a significant reduction in corticosteroid dose when using IVIG. The first study reported a median 8.75 mg (IQR 2.5–17.5, p-value unavailable) daily dose decrease [17] in 8/13 of its patients suffering from SSc associated myopathy by the end of treatment. Similarly, the second study also examined patients suffering from SSc associated myopathy, and noted a 2.5 mg/day difference in steroid requirements between IVIG and placebo group 1 year post treatment ($p < 0.05$) [15]. The third study examined multiple manifestations of SSc, and reported a mean decrease in steroid dosing from 13 mg (±11.6) to 8.9 mg (±10.4) daily (p = 0.01) by the end of IVIG treatment (14.8 ± 19.4 months) [7].

Discussion

This review identified twelve studies with 354 participants examining the effects of IVIG in SSc. These data suggest that IVIG may be effective in treating a range of organ-specific manifestations with minimal side effects, thus making it a potentially attractive therapeutic option for SSc. The data obtained from this study particularly supports the role of IVIG for skin, musculoskeletal and GI manifestations of SSc, with a stabilisation effect demonstrated for respiratory function. However, this review highlights that the current literature regarding IVIG in SSc comprises mostly non-randomised studies with small sample sizes at high risk of bias. Populations and outcome measures were heterogeneous thus precluding a quantitative synthesis. High-quality, randomised clinical trials would assist to confirm the findings of this review.

The majority of included studies demonstrated that a high dose of 2 g/kg/month of IVIG is effective for decreasing skin thickening, as measured through the mRSS. In eight studies reporting the mean difference in mRSS, the improvements exceeded the minimal clinically important difference of 3 – 4 in all patients [36]. This benefit however, is confounded by the fact that mRSS has been shown to spontaneously improve within the first five years of dcSSc onset, even in those receiving placebo, thus making it hard to draw meaningful conclusions regarding the effect of interventional therapy [37].

Although most studies demonstrated an immediate effect weeks after IVIG administration, several studies suggested that repeated dosing may be required, with a greater reduction in mean skin thickness observed after a second dose of IVIG [12], an ongoing benefit of IVIG on skin thickness at 6, 12, 18 and 24 months [14], and the reduction in mRSS being significantly better at 12 rather than 6 months [14]. The population of patients in the latter study were described as having “severe” and “refractory” SSc, suggesting that IVIG may be especially useful for those with intractable disease [14]. This study also provided some evidence for the role of IVIG in halting the progression of DUs, however the number of IVIG cycles and concomitant immunosuppression varied between included studies, with not all reports reaching statistically significant conclusions.

This review also demonstrated the benefit of IVIG on the musculoskeletal manifestations of SSc, with significant improvements in joint pain [19], muscle pain [7], muscle weakness [7,25] and tendon friction rubs [14]. Three studies recorded a significant reduction in serum CK levels, which mirrors various case reports on SSc-overlap syndromes that report improvements as early as one week after IVIG infusion [38-40].

Evidence for benefit of IVIG for upper and lower GI symptoms of SSc was also seen, in some cases after just a single cycle of treatment [25]. This beneficial effect is reinforced by multiple case reports from the literature, which further highlight the ability of IVIG to improve the RDQ and GIT2.0 score, whilst also managing and preventing pseudo-obstruction [41,42]. Some postulate that this effect is due to the ability of IVIG to neutralise the muscarinic-3-receptor autoantibodies that mediate gastrointestinal dysmotility [42], whilst others suggest that the benefit is instead due to normalisation of gut flora [40].

An additional benefit of IVIG seen was the effect on physical function, with three studies reporting benefit [14,16,19], though only two were statistically significant [16,19]. The improvement in HAQ was demonstrated in patients suffering from a range of different SSc manifestations, thus making it hard to discern one likely cause for this. One possibility may be related to the reduction in muscle weakness and joint pain seen in this review, which makes it easier for patients to carry out activities of daily living, thus improving their functionality. Only one study did not demonstrate improvement in HAQ, possibly because some patients received only one dose of IVIG, compared to the other studies in which multiple doses were administered [12]. A less established role of IVIG is its corticosteroid-sparing effect, which was demonstrated in three studies [7,15,17] across multiple organ manifestations, though most notably for SSc associated myopathy, thus confirming similar effects found in the literature regarding the effect of IVIG in other CTDs [38]. Prolonged steroid use increases the risk of multiple undesired adverse effects including diabetes [43], osteoporosis [44], and immunosuppression [45], thus it is important to consider therapies with demonstrated steroid-sparing effect as a key therapeutic option in rheumatological disease. This is of particular note in SSc patients, as avoidance of high dose steroids is critical in reducing the risk of scleroderma renal crisis, and its associated complications.

A major contributor to mortality in SSc is interstitial lung disease [4]. In this review IVIG showed minimal effect in improving pulmonary function; only one study reported a statistically significant improvement in DLCO and 6MWT [21], but there were no differences in other PFT parameters, radiographic CT changes, NYHA score or 6MWT. This stabilisation in DLCO and FVC, rather than the decline usually seen in SSc, may be considered a positive finding in itself. This is reflected in the therapeutic target for many anti-fibrotic drugs [46], which aim to preserve rather than restore pulmonary function and to reduce the rate of PFT results decline [47]. Overall, these findings are in contrast to a case report that noted clinical and radiological improvement post IVIG [23], but is in keeping with another study that noted progression of pulmonary disease despite IVIG therapy [48]. Overall, the evidence suggests that the benefit of IVIG in pulmonary SSc remains unclear.

Most of the adverse effects associated with IVIG administration were minor, such as nausea, dizziness, fever and rash. This is aligned with the literature which cites mild side effects in 30–60 % of IVIG patients [49,50]. More serious adverse effects associated with IVIG in this study included two cases of AKI, two cases of systemic hypertension, two cases of aseptic meningitis, one case of haemolytic anaemia, one case of thromboyctopenia, one TIA, one cardiac arrest, one case of a dermatological reaction and one of DVT. Notably, the current risk of thromboembolism may be reduced since the removal of thromboembolic agents from IVIG preparations since 2009 [51]. The risk of more serious events such as these has been described in 4.5 % of patients [49,50]. Although one study suggested the risk of adverse events is reduced in IVIG monotherapy [25], IVIG is an expensive and limited resource [52], as it relies on plasma donations from volunteers, and thus may not be readily accessible for all patients.

To our knowledge, our study is the only one to systematically review the effect of IVIG by multiple organ manifestations, thereby providing a clinically relevant summary of the literature. We have also sought to comprehensively appraise all relevant literature over the past 20 years, with no discrimination on the dose or method of IVIG infusion. The findings from the RCT by Takehara et al. [12], which was the highest quality study in this review, show particular promise for the effect of IVIG on improving mRSS and DFT, whilst the non-significant findings on pulmonary function tests and HAQ are less conclusive.

The limitations of this review include the significant heterogeneity and limited quality amongst included studies - only one RCT was assessed at moderate risk of bias and the remaining non-randomised trials were deemed at high risk of bias when considering sample size and methodology. The retrospective nature of many studies resulted in the inclusion of patients with variable disease severity and duration, making comparison between like patients difficult. Many patients received concomitant immunosuppressants, rendering the individual effect of IVIG difficult to assess. Fifty-nine patients (22 %) suffered from SSc-overlap syndromes, which although makes it hard to discern where IVIG is having an effect, is clinically relevant as it mimics the real-life patient population and is of relevance to multinational cohorts with phenotypic differences. Finally, our search was limited to English language articles, thus potentially missing data published in multinational or phenotypically diverse populations of SSc [53].

Conclusion

This study provides evidence to support the use of IVIG as an effective steroid-sparing agent, in the management of cutaneous,

musculoskeletal, and GIT manifestations of SSc, particularly as an adjunct or additional therapy for refractory disease. When administered according to recommended guidelines, the risk of serious adverse events is low, highlighting IVIG as a potentially attractive option for SSc treatment. However its high cost and limited availability may act as a barrier to more widespread utilisation. Included studies were small and of poor quality, and whilst large double-blind RCTs are desirable to confirm these effects and inform the development of consensus guidelines for IVIG use, given the rarity and heterogeneity of SSc, such studies may be difficult to conduct.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152471.

References

[1] Dumoitier N, Lofek S, Mouthon L. Pathophysiology of systemic sclerosis: state of the art in 2014. La Presse Médicale 2014;43(10):e267–78.
[2] Fallet B, Walker UA. Current immunosuppressive and antifibrotic therapies of systemic sclerosis and emerging therapeutic strategies. Expert Rev Clin Pharmacol 2020;13(11):1203–18. https://doi.org/10.1080/17512433.2020.1832466.
[3] Czirjak L, Foeldvari I, Müller-Ladner U. Skin involvement in systemic sclerosis. Rheumatology 2008;47(suppl_5):v44–5.
[4] Gomes JP, Santos L, Shoenfeld Y. Intravenous immunoglobulin (IVIG) in the vanguard therapy of systemic sclerosis. Clin Immunol 2019;199(c90, 100883537): 25–8. https://doi.org/10.1016/j.clim.2018.12.006.
[5] Frech TM, Shanmugam VK, Shah AA, et al. Treatment of early diffuse systemic sclerosis skin disease. Clin Exp Rheumatol 2013;31(2 Suppl 76):166–71.
[6] Cantarini L, Rigante D, Vitale A, et al. Intravenous immunoglobulins (IVIG) in systemic sclerosis: a challenging yet promising future. Immunol Res 2015;61: 326–37.
[7] Sanges S, Riviere S, Mekinian A, et al. Intravenous immunoglobulins in systemic sclerosis: data from a French nationwide cohort of 46 patients and review of the literature. Autoimmun Rev 2017;16(4):377–84. https://doi.org/10.1016/j.autrev.2017.02.008.
[8] Kivity S, Katz U, Daniel N, Nussinovitch U, Papageorgiou N, Shoenfeld Y. Evidence for the use of intravenous immunoglobulins—A review of the literature. Clin Rev Allergy Immunol 2010;38:201–69.
[9] Hachulla E, Wibaux A, Hatron P, et al. Home sequential high dose intravenous immunoglobulins in systemic autoimmune disease. Ann Rheum Dis 2002;61(3): 277–8.
[10] Katz U, Achiron A, Sherer Y, Shoenfeld Y. Safety of intravenous immunoglobulin (IVIG) therapy. Autoimmun Rev 2007;6(4):257–9.
[11] Levy Y, Sherer Y, Langevitz P, et al. Skin score decrease in systemic sclerosis patients treated with intravenous immunoglobulin–a preliminary report. Clin Rheumatol 2000;19:207–11.
[12] Takehara K, Ihn H, Sato S. A randomized, double-blind trial of intravenous immunoglobulin in diffuse cutaneous systemic scleros. Ann Rheumatic Dis 2013;71 (SUPPL. 3). https://doi.org/10.1136/annrheumdis-2012-eular.232.
[13] Szekanecz Z, Aleksza M, Antal-Szalmás P, et al. Combined plasmapheresis and high-dose intravenous immunoglobulin treatment in systemic sclerosis for 12 months: follow-up of immunopathological and clinical effects. Clin Rheumatol 2009;28:347–50.
[14] Poelman CL, Hummers LK, Wigley FM, Anderson C, Boin F, Shah AA. Intravenous immunoglobulin may be an effective therapy for refractory, active diffuse cutaneous systemic sclerosis. J Rheumatol 2015;42(2):236–42. https://doi.org/10.3899/jrheum.140833.
[15] Chaigne B, Benmostefa N, Rodeia S, et al. Corticosteroid-sparing benefit of intravenous immunoglobulins in systemic sclerosis-associated myopathy: a retrospective study of 52 patients. J Scleroderma Relat Disord 2018;3(Supplement 1):206. https://doi.org/10.1177/2397198317753474.
[16] Levy Y, Amital H, Langevitz P, et al. Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: an open-label study. Arthritis Rheum 2004;50(3):1005–7.
[17] Raja J, Nihtyanova SI, Ong VH, Denton CP. An observational study of intravenous immunoglobulin therapy in the treatment of gastrointestinal involvement in systemic sclerosis. Rheumatology 2015;54(Supplement 1):i161. https://doi.org/10.1093/rheumatology/kev090.052.
[18] Jaime JLT, Castillo AG, Simeon-Aznar CP, et al. Use of intravenous immunoglobulin therapy in patients with systemic sclerosis: a spanish multicenter experience. Ann Rheum Dis 2019;78(Supplement 2):856. https://doi.org/10.1136/annrheumdis-2019-eular.2762.
[19] Nacci F, Righi A, Conforti ML, et al. Intravenous immunoglobulins improve the function and ameliorate joint involvement in systemic sclerosis: a pilot study. Ann Rheum Dis 2007;66(7):977–9.
[20] Agostini E, De Luca G, Bruni C, et al. Intravenous immunoglobulins reduce skin thickness in systemic sclerosis: evidence from Systematic Literature Review and from real life experience. Autoimmun Rev 2021;20(12):102981. https://doi.org/10.1016/j.autrev.2021.102981.
[21] Perkovic D, Petric M, Bozic I, et al. Low dose intravenous immunoglobulin in addition to cyclophosphamide in systemic sclerosis: single centre experience. Wien Klin Wochenschr 2021;133(19–20):1070–5. https://doi.org/10.1007/s00508-020-01669-y.
[22] Ihn H, Mimura Y, Yazawa N, et al. High-dose intravenous immunoglobulin infusion as treatment for diffuse scleroderma. Br J Dermatol 2007;156(5):1058–60.
[23] Mauhin W, Rivière S, Cabane J, Tiev K. Improvement in lung fibrosis using intravenous immunoglobulin in systemic sclerosis with myositis. Scand J Rheumatol 2014;43(2):170–1.
[24] Matsuda KM, Sugimoto E, Ako Y, et al. Reliability, validity, and sensitivity of the Japanese version of the University of California Los Angeles scleroderma clinical trial consortium gastrointestinal tract instrument: application to efficacy assessment of intravenous immunoglobulin administration. J Dermatol 2024. https://doi.org/10.1111/1346-8138.17202. Apr 1.
[25] Tandaipan J, Guillen-Del-Castillo A, Simeon-Aznar CP, et al. Immunoglobulins in systemic sclerosis management. A large multicenter experience. Autoimmun Rev Nov 2023;22(11):103441. https://doi.org/10.1016/j.autrev.2023.103441.
[26] Hoogen F., Khanna D., Fransen J., et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European league against Rheumatism collaborative initiative. 2013.
[27] Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane handbook for systematic reviews of interventions. 2019. p. 205–28.
[28] Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016:355.
[29] Doyle D, Dieppe P, Scott J, Huskisson E. An articular index for the assessment of osteoarthritis. Ann Rheum Dis 1981;40(1):75–8.
[30] Boonstra AM, Preuper HRS, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. Internat J Rehabilit Res 2008;31(2):165–9.
[31] Landon-Cardinal O, Devilliers H, Chavarot N, et al. Responsiveness to change of 5-point MRC scale, endurance and functional evaluation for assessing myositis in daily clinical practice. J Neuromuscul Dis 2019;6(1):99–107. https://doi.org/10.3233/JND-180358.
[32] Doré A, Lucas M, Ivanco D, Medsger Jr TA, Domsic RT. Significance of palpable tendon friction rubs in early diffuse cutaneous systemic sclerosis. Arthritis Care Res 2013;65(8):1385–9.
[33] Shaw M, Dent J, Beebe T, et al. The Reflux Disease Questionnaire: a measure for assessment of treatment response in clinical trials. Health Qual Life Outcomes 2008;6:1–6.
[34] Zampatti N, Garaiman A, Jordan S, et al. Performance of the UCLA scleroderma clinical trials consortium gastrointestinal tract 2.0 instrument as a clinical decision aid in the routine clinical care of patients with systemic sclerosis. Arthritis Res Ther 2021;23(1):1–11.
[35] Bruce B, Fries JF. The health assessment questionnaire (HAQ). Clin Exp Rheumatol 2005;23(5 Suppl 39):S14–8. Sep-Oct.
[36] Khanna D, Clements PJ, Volkmann ER, et al. Minimal clinically important differences for the modified rodnan skin score: results from the scleroderma lung studies (SLS-I and SLS-II). Arthritis Res Ther Jan 16 2019;21(1):23. https://doi.org/10.1186/s13075-019-1809-y.
[37] Denton C.P. Challenges in systemic sclerosis trial design. *Semin Arthritis Rheum*. Dec 2019;49(3S):S3–S7. doi:10.1016/j.semarthrit.2019.09.019.
[38] Wang DX, Shu XM, Tian XL, et al. Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: a systematic literature review. Clin Rheumatol 2012;31:801–6.

[39] Danieli MG, Calcabrini L, Calabrese V, Marchetti A, Logullo F, Gabrielli A. Intravenous immunoglobulin as add on treatment with mycophenolate mofetil in severe myositis. Autoimmun Rev 2009;9(2):124–7.
[40] Kamei R, Yamaoka T, Ikinaga K, Murota H, Shimizu K, Katayama I. Successful treatment of a refractory dysbiotic intestinal pseudo-obstruction in a patient with systemic sclerosis-polymyositis overlap syndrome by intravenous immunoglobulin administration possibly related to gut flora normalisation. Clin Exp Rheumatol 2017;35(4):214–5.
[41] Clark K, Etomi O, Denton C, Ong V, Murray C. Case report Intravenous immunoglobulin therapy for severe gastrointestinal involvement in systemic sclerosis. Clin Exp Rheumatol 2015;33(91):S168–70.
[42] Kumar S, Singh J, Kedika R, et al. Role of muscarinic-3 receptor antibody in systemic sclerosis: correlation with disease duration and effects of IVIG. Am J Physiol-Gastrointest Liver Physiol 2016;310(11):G1052–60.
[43] Angelopoulos TP, Tentolouris NK, Bertsias GK, Boumpas DT. Steroid-induced diabetes in rheumatologic patients. Clin Exp Rheumatol 2014;32(1):126–30.
[44] Sinigaglia L, Varenna M, Girasole G, Bianchi G. Epidemiology of osteoporosis in rheumatic diseases. Rheumatic Dis Clinics 2006;32(4):631–58.
[45] Cheng J, Li JB, Sun QL, Li X. Reactivation of hepatitis B virus after steroid treatment in rheumatic diseases. J Rheumatol 2011;38(1):181–2.
[46] Allanore Y, Khanna D, Smith V, et al. Effects of nintedanib in patients with limited cutaneous systemic sclerosis and interstitial lung disease. Rheumatology (Oxford) Jun 9 2023. https://doi.org/10.1093/rheumatology/kead280.
[47] Vonk MC, Smith V, Sfikakis PP, Cutolo M, Del Galdo F, Seibold JR. Pharmacological treatments for SSc-ILD: systematic review and critical appraisal of the evidence. Autoimmun Rev Dec 2021;20(12):102978. https://doi.org/10.1016/j.autrev.2021.102978.
[48] Naqvi SB, Kim HJ. Interstitial lung disease (ILD) Responsive To Rituximab and not standard immunosuppression-A case presentation. D101 case REPORTS: interstitial lung disease and diffuse alveolar hemorrhage. American Thoracic Society; 2013. p. A5789. -A5789.
[49] Brannagan TH, Nagle KJ, Lange DJ, Rowland LP. Complications of intravenous immune globulin treatment in neurologic disease. Neurology 1996;47(3):674–7.
[50] Stangel M, Kiefer R, Pette M, Smolka MN, Marx P, Gold R. Side effects of intravenous immunoglobulins in neurological autoimmune disorders: a prospective study. J Neurol 2003;250:818–21.
[51] Lidar M, Masarwa S, Rotman P, Carmi O, Rabinowicz N, Levy Y. Intravenous immunoglobulins for rheumatic disorders and thromboembolic events-a case series and review of the literature. Immunol Res 2018;66(6):668–74. https://doi.org/10.1007/s12026-018-9047-y.
[52] Wilson K, Hébert PC. The challenge of an increasingly expensive blood system. Cmaj 2003;168(9):1149–50.
[53] Moore DF, Steen VD. Racial disparities in systemic sclerosis. Rheumatic Dis Clin 2020;46(4):705–12.