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Review

Intravenous immunoglobulins reduce skin thickness in systemic sclerosis: evidence from Systematic Literature Review and from real life experience

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ABSTRACT

Introduction: Intravenous immunoglobulins (IVIG) are a new therapeutic approach in systemic sclerosis SSc. An immunomodulatory and antifibrotic activity has been postulated. IVIG are generally well tolerated and have only rare side effects. Our retrospective study focused its attention on SSc, an autoimmune connective tissue disease, characterized by several complications which has a significant impact on patient's quality of life. The patho-physiology comprises fibrotic, vascular and immunological aspects.

Aim: The aim of this study was to verify the effectiveness of IVIG on SSc skin involvement. Moreover, a systematic review of the literature (SLR) of the results obtained to date on the use of Intravenous immunoglobulin (IVIG) in SSc has been also performed.

Patients and methods: The data of 24 patients (21 women, 3 male) with refractory diffuse SSc skin involvement were evaluated (mean age was 52.13 years). IVIG infusion at a dosage of 2 g/Kg body weight for 4 consecutive days/month, was started between 2002 and 2019. Skin involvement was evaluated with the modified Rodnan Skin Score (mRSS) before therapy and then again after 6 and 12 months. To perform the SLR, the PubMed, Medline, Embase, and Web of Science database were searched from 1990 to 2020 (keywords: IVIG, systemic sclerosis). Three assessors (E.A., C.B. & M.M.C) identified the criteria to scan all papers.

Results: From the total SLR (106 results), 17 papers were identified after the separation of the clinical cases from the studies (total number of treated patients 183). The studies were classified according to the organ involvement considered in each study, as well as the prescribed dose (high or low doses), and the therapeutic regimens. In the selected papers, the organs mainly involved were the skin, the gastrointestinal, the joint and the cardiovascular systems. Only in one case, plasmapheresis was associated to IVIG. All papers reported significant reduction of the skin involvement, although generally the strength of the works was limited the lack of control cases or by the low number of patients involved.

From the real life experience, a statistically significant reduction of mRSS was obtained at 6 months follow-up (average value of -6.61 ± 5.2, $p < 0.001$), and it was further maintained with a significant stabilization after 12-months (-11.45 ± 9.63, $p < 0.002$).

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Discussion: This SLR and the data of the retrospective study suggest that IVIG may improve skin involvement reducing mRSS in particular in those patients that were refractory to other standard of care therapies and represents a therapeutic option in patients with concomitant myositis. The literature review revealed encouraging perspectives on the use of this therapy, given the effectiveness found in the selected works.

1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease leading to skin and internal organs fibrosis, characterized by endothelial damage, alteration of the cellular and humoral immunity, and abnormal collagen production [1–4]. The treatment of SSc has often been proved to be ineffective on skin involvement, while recently some evidence of efficacy of antiproliferative and anti IL6 on interstitial lung disease (ILD) has been provided [5–10].Today, intravenous immunoglobulins (IVIG) are part of a standard of care treatment of different autoimmune diseases [11], but their main mechanism of action is not yet fully understood. It can be mainly attributed to the activity of IgG, but the immune modulatory activity of the other components present in IVIG may also be involved [2]. Thus, more than one pathway seems to contribute to the immunomodulatory effect which is obtained in many autoimmune diseases that benefit from IVIG therapy [2,5]. The use of IVIG is now limited to a series of indications, since new biological and immunomodulatory therapies are emerging in this field. Nevertheless, IVIG can be a useful choice in patients refractory to first-line therapies and in those where disease modifying treatments were not tolerated.

In SSc, the use of IVIG has been suggested by several studies [12,13] with a peculiar efficacy in refractory cases, and in cutaneous, gastrointestinal [14–18] and joint involvement [19–23]. The reported efficacy may be explained by the fact that the significant involvement of inflammatory cytokines (IL-6, IL-13), B cells and of TGFβ in SSc pathogenesis [1], may constitute a substrate for IVIG activity [6,24].

The aim of the present work was to perform a Systematic Literature Review (SLR) on the use of IVIG in SSc and to report our experience on the effect of IVIG on skin involvement in a cohort of SSc patients refractory to standard therapy.

2. Patients and methods

2.1. Systematic literaure review

2.1.1. Data sources and search

A SLR was performed to search for papers that concerned IVIG us in SSc. The words “IVIG”, “systemic sclerosis”, and “scleroderma” were chosen and the PubMed, Medline, Embase, and Web of Science databases were searched from 2000 to 2020 three assessors (E.A., C.B. & M. M.C) identified the criteria to scan all papers. Moreover, references from selected works and reviews, were also searched.

2.1.2. Study selection

The assessors independently evaluated the identified works, and as first step titles and abstract were screened, and thereafter texts were evaluated. The exclusion criteria were the following: abstracts in congresses; non-relevance, either because they did not concern the SSc or because they did not concern the treatment with IVIG; did not deal with cases of treated patients, even though the content was relevant to the IVIG and SSc theme; papers not written in English. No restrictions were set on study quality, design or follow-up. Disagreements were resolved by consensus, and when consensus was not reached, the evaluation of a third assessor (C.B) was asked.

Quality assessment, data extraction, synthesis and analysis.

From selected works, study design, subject characteristics and study results were extracted. The quality of the works (SSc classification, method of patient selection, evaluation of outcome) was evaluated with the Critical Appraisal Skills Program (http://www.casp-uk.net). Hazard ratios and odds ratio for predictors were collected, as well as *p*-values. The heterogeneity of the retrieved papers and data did not allow a

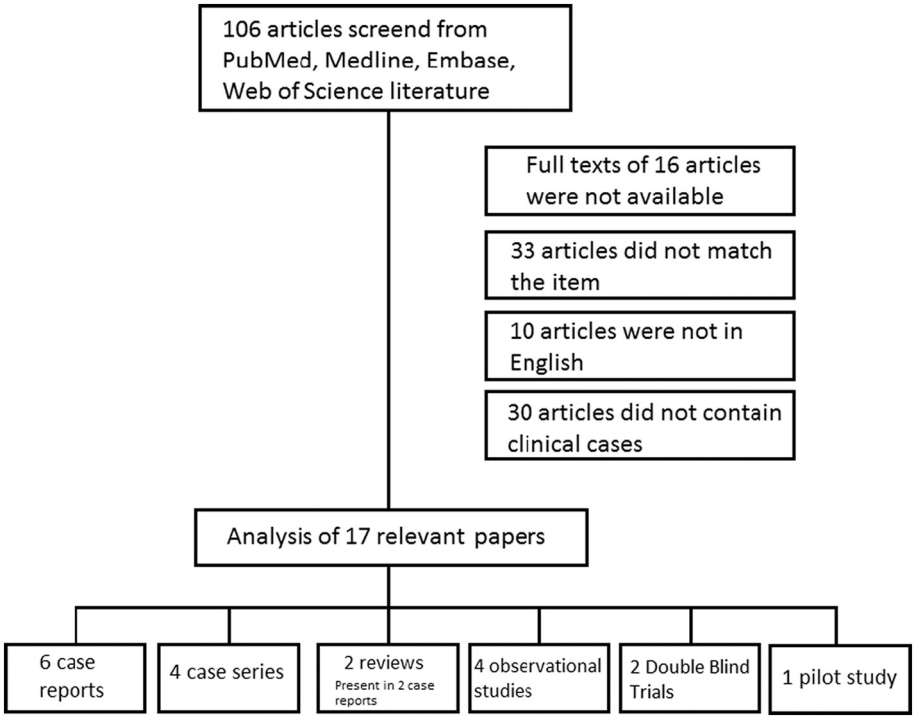

Fig. 1. Sistematic Literature Review flow chart.

formal meta-analysis. Prisma methodology was followed (Fig. 1).

2.2. Data from real life experience

The data from 24 patients with refractory diffuse SSc patients (mean age 52.13 years), that previously failed standard of care treatments, were identified in the Scleroderma Unit AOUC in Florence and in the UNIRAR of the San Raffaele Hospital in Milano. All patients underwent clinical evaluation at baseline, and at 6 and 12 months: skin involvement was measured with the mRSS [25], lung function with pulmonary function tests [26], chest computed tomography (CT) [27] and auto-antibody profile screening (ANA, ACA, Scl70, RNA polIII, AntiPM/Scl) were carried out at baseline only.

The study was approved by the Ethical Committee of the Tuscan Region.

3. Results

3.1. Systematic literature review

Out of 106 identified papers, only 17 papers fulfilled the criteria with a total of 182 patients studied (136 female, 25 remain unspecified). The selected texts were categorized according to the type of study: case report (6); case series (4); retrospective observational studies (4); Double blind, placebo controlled, clinical trial (DBT) (2); pilot study (1).

In the individual works, the effectiveness of therapy in the involved areas was highlighted. The skin was the main focus, but also gastrointestinal, articular, cardiac, pulmonary and renal involvement were also assessed. Subsequently, complications were also recorded, thus assessing also the safety of IVIG therapy. Moreover, the most common dosages have been compared, from 0.4 g/Kg/month (low dose) to 2 g/Kg/month (high dose), and for how many cycles IVIG were administered.

A retrospective observational study by Sanges et al. [15], was performed on 46 patients treated with infusion of IVIG at the dosage >1 g/kg/month. The skin, pulmonary, renal, digestive, joint and muscular district were evaluated and the data collected at the baseline and follow-ups. A significant improvement of muscle pain (74% vs. 20%, p b 0.0001), muscle weakness (45% vs. 21%, $p = 0.01$), joint pain (44% vs. 19%, $p = 0.02$), CK levels (1069 ± 1552 UI vs. 288 ± 449 UI, p b 0.0001) and CRP levels (13.1 ± 17.6 mg/L vs. 9.2 ± 16.6 mg/L, $p = 0.001$) was observed. In particular, an improvement of gastro-esophageal reflux disease (68% vs. 53%, $p = 0.06$) and bowel symptoms (42% vs. 27%, p = 0.06) was noted, while lung and skin involvement remained stable. A remark is the fact that corticosteroid daily dose was significantly lowered by the end of treatment (13.0 ± 11.6 mg/day vs. 8.9 ± 10.4 mg/day, p = 0.01 [15]. Two adverse events were reported: a deep vein thrombosis and a diffuse edematous syndrome [15]. In the study conducted by Perković et al. [28] 9 SSc patients, refractory to previous therapies and with lung and skin infections, were treated with a low-dose IVIG (0.4 g/Kg/month) treatment for at least 3 cycles. Healing of digital ulcers (DU) and a decrease of mRSS was recorded in 3 patients, and an increase of carbon monoxide diffusion capacity in other 3 patients [28], but 1 patient presented a radiological progression of ILD [28]. The IVIG infusion was well tolerated and no adverse reactions were observed [12,28].

Other studies have focused on peculiar organ involvement in SSc. Nacci et al. [22] conducted a pilot study of 7 SSc patients treated with high doses of IVIG (2 g/Kg/4 days/month) for 6 months for refractory joint involvement which did not respond to previous therapy with methotrexate and cyclophosphamide [22]. After 6 months of therapy, joint pain and tenderness, measured with the VAS, decreased significantly (p,0.03), hand function (IAFD) improved significantly (p,0.02) as well as quality of life (HAQ; p,0.03), and in particular mRSS was significantly reduced (p,0.003) [22]. Only 1 patient did not show any improvement and no adverse reaction was observed. Raja et al. [18] treated 15 SSc and overlap polymyositis patients refractory to conventional disease-modifying agents with IVIG treatment at a dose 2 g/Kg/month: they obtained a significant reduction in gastro-esophageal reflux frequency and intensity mean scores (=p 0.006 and $p = 0.013$, respectively, and of the Gastrointestinal Tract (GIT) 2.0 score (from 1.07 (S.D. 0.67) to 0.60 (0.46), $p = 0.002$) [18]. Moreover, Medical Research Council sum score and creatine kinase level were reduced ($p = 0.001$ and $p = 0.025$, respectively) as well as of mRSS (from 21.5 (S.D. 13.8) to 10 (10.6), $p = 0.005$) [18] without any adverse events. Poelman et al. [29] carried out a retrospective study on 30 refractory active dSSc treated with IVIG with 2 g/Kg/month, and analyzed the change in mRSS, compared to the baseline, in subsequent follow-ups to 6, 12, 18 and 24 months. To increase the statistical strength of their paper they compared the mRSS data to 6 and 12 months with from 3 other clinical trials in which treatments were not effective as negative control groups [29]. Concomitant immunomodulatory or anti-fibrotic therapies included mycophenolate mofetil (70%), prednisone (33.3%), cyclophosphamide (20%), methotrexate (10%), imatinib (3.3%) and hydroxychloroquine (3.3%). At 6 months, the mean baseline mRSS of 29.6 ± 7.2 significantly decreased to 24.1 ± 9.6 ($N = 29$; $p = 0.0011$) and then to 22.5 ± 10.0 ($N = 25$; $p = 0.0001$) at 12 months, 20.6 ± 11.8 ($N = 23$; p = 0.0001) at 18 months and 15.3 ± 6.4 ($N = 15$; $p < 0.0001$) at 24 months. The mean change in mRSS at 6 months was not significantly different in the IVIG group (−5.3 ± 7.9) compared to the Relaxin (−4.8 ± 6.99, $p = 0.74$) or MMF group (−3.4 ± 7.4, $p = 0.26$). However, at 12 months the mean change in mRSS was significantly better in the IVIG group (−8 ± 8.3) than in the D-pen (−2.47 ± 8.6, $p = 0.005$) and Collagen (−3.4 ± 7.12, p = 0.005) groups and was comparable to the group of primary MMF responders (−7.1 ± 9, $p = 0.67$) [29]. In this observational study, the authors suggest the effectiveness of IVIG in patients refractory to previous therapies with a long-term cutaneous beneficial outcome [29]. Some adverse events were more frequently observed (12 headaches, 7 fatigue, 4 nausea and/or emesis, 3 arthralgias and/or myalgias, 3 rash and/or pruritus) while others were more rare (diarrhea, leukopenia, transient ischemic attack, paplpitations, dyspnea, hypertension, decreased appetite, acute kidney injury). In some cases these led to therapy discontinuation.

In 63 dcSSc patients, Takehara et al. [30] in a randomised, double-blind, placebo-controlled trial administered IVIG 400 mg/kg/day for 5 days in a single single course versus placebo: IVIG was administered only to those with less than a 5-point improvement (readministration study) [30]. For the first endpoint, no changes in the mRSS (IVIG −3.3 ± 4.2 vs −4.2 ± 4.6 in placebo) were observed [30]. In the readministration study, the change of the MRSS at 60 weeks after the first administration was −8.3 ± 1.0 in patients with 2 courses of IVIG vs −4.1 ± 1.1 in the group treated with a single course of IVIG ($p = 0.0040$) [30]. Adverse drug reactions were 38.9% in the first course and 31.6%, in the second one [30]. This paper is the first one which clearly shows that repeated IVIG administrations are significantly efficacious on skin involvement.

In an interesting case, Szekanecz et al. [31] treated a patient with a combination of 3 repeated plasmapheresis with the removal and reinfusion of 1000 ml plasma, and 15 g hIVIG every month, obtaining a control of the disease progression with a significant improvement of the mRSS and Capillaroscopic pattern. No adverse effects were reported [31]. Mauhin et al. [32] described the treatment of a 53 yr. old SSc patient with ILD and myopathy. Her symptoms were dyspnoea, swallowing disorders, and proximal muscle weakness. At diagnosis, chest high-resolution computed tomography (HRCT) showed diffuse subpleural ground glass opacities with septal thickening in the lungs suggesting non-specific interstitial pneumonia (NSIP). Bronchoalveolar lavage fluid was sterile with lymphocytic alveolitis. Before the start of the treatment she presented increased levels of muscular enzymes in serum (creatine kinase: 1224 U/L (upper limit <195 UL). aspartate transaminase: 150 U/L (upper limit <35 U/L); aldolase: 19 U/L. (upper limit <7 UL). She had an impaired forced vital capacity (FVC 53% of the predicted value) and diffusing capacity of the lung for carbon monoxide

(DLCO 50% of the predicted value), while echocardiography revealed normal left ventricular function and systolic pulmonary artery pressure (35 mmHg) [32]. She was treated with six IVIG cycles at 2 g/Kg/month combined with azathioprine with recovery of muscle strength and a complete regression of NSIP at HRCT. Adverse reactions were not reported [32]. C. Cacciatore et al. [33] reported a case of a 48 yr. old woman with SSc and severe heart failure, supraventricular arrhythmias and symptomatic pericarditis, which required surgical intervention and immunosuppressive drugs (steroids with rituximab), without improvement. She received a treatment with IVIG at a dosage of 0,4 g/Kg/month, maintaining 10 mg/day of prednisone, with a progressive the improvement of dyspnoea (from 3 to 1 stage NYHA), of heart systolic ejection fraction (from 25% to 45%), BNP of 590 a 47 ng/ml and decrease of mRSS (from 24 to 18 after 3 courses). After 18 months she was stable, without disease progession [33], and no adverse events were experienced. Four papers focused on gastrointestinal involvement which is one of the major causes of morbidity in SSc. Clark et al. [17] described two SSc patients with myositis and severe GI involvement. One patient was a 43 yr. old woman with left ventricular failure and rapidly progressive skin involvement (Modified Rodnan skin score increased from 19/51 to 29/51 in 5 months) and severe GI symptoms such nausea, intermittent vomiting, weight loss, abdominal bloating alternating diarrhoea with constipation. She presented with increasing muscle weakness and lung involvement (falling volumes 68.3% predicted FVC from 91% over 1 year) [17]. She was refractory to all treatments and was started on IVIG at a dose of 2 g/kg/month. After the treatment MRGE symptoms were reported less than once a week. The UCLA SCTC GIT 2.0 score was 2.75 pre-treatment, 11.5 after months, and then finally 2.05 [17]. The second patient was a 48 yr. old man with dcSSc with skin involvement, cardiac involvement with arrhythmias, peripheral edema and elevated troponin, GI symptoms including dysphagia, severe acid reflux, slow gastric emptying and early satiety abdominal bloating and significant diarrhoea, with a 40 kg weight loss. There was evidence of esophagitis on endoscopy, and CT scanning showed dilated stomach and small bowel with no obstruction. Positive hydrogen breath testing suggested small bowel overgrowth [17]. IVIG at a dose of 2 g/kg was useful was administered his UCLA SCTCGIT 2.0 scores improved from 1.69 to 1.25 and he remained stable without adverse events [17]. Chinniah and Girish M Mody [14] reported 56 yr. old SSc patient who had an amelioration GI symptoms after high doses of corticosteroids, azathioprine and two doses of IVIG and improved further when rituximab was added [14]. Kamei et al. [16] described a case of SSc-PM overlap syndrome and a peculiar dysbiotic intestinal pseudo-obstruction dysphagia which ameliorated significantly after IVIG at 0.4 g/Kg/day [16] without adverse events. Asano et al. [34] described a case of 60 yr. old patient who received IVIG 0.4 g/kg/month [34]: The patient improved dramatically with reduction of the mRSS from 22 to 17 at 2 weeks and 14 at 4 weeks, progressively improving over 2 yrs. (to mRSS 7) without side effects. The skin biopsies obtained before and after weeks after IVIG, showed that skin thickness was reduced from 2.8 to 2.0 mm, while the expression of TGF-β receptors and α-SMA were significantly reduced after IVIG to levels similar to those observed in normal fibroblasts. This evidence may suggest that IVIG can also be efficacious in changing the myofibroblast phenotype [34]. Moreover, they also reported 3 SSc cases that after IVIG markedly improved mRSS without side effects [34]. Among 32 patients treated by Scarpone et al. [21], a SSc patient refractory to cyclophosphamide, methotrexate and glucocorticoids, received 8 cycles of 2 g/kg/monthly IVIG along with methotrexate with a significant skin improvement measured with mRSS [21]. Amital et al. [19] treated 2 SSc refractory patients with 6 cycles of IVIG obtaining a decrease in mRSS (from 26 to 16 and from 34 to 20, respectively) [19]: another patient responded to 3 cycles of IVIG with a decrease of mRSS from 32 to 20 and an increment of carbon monoxide transfer factor from 70% to 84% [19].

In the paper of Lidar et al. [35], attention was drawn to thromboembolic events as adverse effect related to IVIG therapy. In fact, this study describes 9 patients who experienced thromboembolic events: 6 of them were dcSSc that were include in a group of 20 SSc patients treated with a slow infusion IVIG (8 h) at a dose of 0.4 g/Kg/month [35]. In their review, it is stated that severe adverse events such as myocardial infarction [36–38], cerebrovascular accident [37], deep vein thrombosis and pulmonary embolism [39,40] as well as thrombosis in unusual sites (internal jugular [41] vein and the superior vena cava [42]). Acute renal failure, exacerbation of congestive heart failure and/or thromboembolic phenomena may occur in up to 4.5% of patients treated with IVIG [43,44]. Paran et al. [39] reviewed the clinical characteristics, risk factors, and outcome of patients sustaining a thrombotic event coincident with IVIG administration. They reported that arterial thrombosis (stroke and myocardial infarction) are four times more frequent than venous thrombosis (deep vein thrombosis and pulmonary embolism) [39]. Arterial thrombosis tends to occur earlier after IVIG administration (77% within 24 h) than venous thrombosis (54% more than 24 h after IVIG administration) and is associated with advanced age and atherosclerotic vascular disease, while venous thrombosis is associated with factors contributing to venous stasis such as obesity and immobility [35]. SSc is not typically associated with a propensity for thromboembolism unless complicated by secondary APS [45]. It may be postulated that the a priori reduced blood flow in vessels of SSc patients, already stenosed from media/intimal hyperplasia, combined with increased plasma viscosity and enhanced platelet activation associated with IVIG infusions [35]. An important aspect to highlight is that this study recollects data from patient treated between the years 1996–2009, and that none occurred in rheumatic patients receiving IVIG between the years 2009–2017, probably due to a safer formulation of the product, after removal of thrombosis-generating agents [35].

3.2. IVIG treatment, experience from real life

Our team collected and examined the data of 24 patients (21 women 3 male), with refractory dcSSc patients (mean age 52.13 years) and/or concomitant refractory skeletal myositis, unresponsive to previous standard of care therapies (Table 1. The mean change from baseline to 6 and 12 months was significant (Fig. 2). Versus baseline, at 6 months

Table 1
Patients characteristics.

Patient	Age	ANA	ACA	Scl70	RNA polIII	AntiPM/Scl
1	53	pos	pos cenpB	neg	Neg	neg
2	49	pos 1:640	Neg	pos	Neg	neg
3	61	pos 1:1280	Pos	neg	Neg	neg
4	43	pos 1:640	Neg	pos		neg
5	29	pos 1:640	Neg	pos	Neg	neg
6	30	pos 1:640		pos		
7	33	pos 1:640		pos	Neg	neg
8	62	pos 1:320	Pos			
9	49	pos 1:640	pos cenpA,B			
10	63	pos 1:640		pos	Neg	neg
11	71	pos 1:640		neg	Neg	neg
12	65	pos 1:320				
13	77	pos 1:2560		neg	Pos	neg
14	42	pos	Neg	pos		
15	59	pos 1:2560	Neg	pos	Neg	neg
16	49	pos	Neg	pos		neg
17	77	pos	Pos	neg	Neg	neg
18	25	pos		pos		
19	53	pos 1:160				
20	39	pos >1:640 (anti-RNP)	Neg	neg	Neg	neg
21	65	pos 1:640	Pos	neg	Neg	neg
22	63	pos 1:640	Neg	pos	Neg	neg
23	47	pos 1:640	Neg	pos	Neg	neg
24	47	pos 1:1280	Neg	pos	Neg	neg

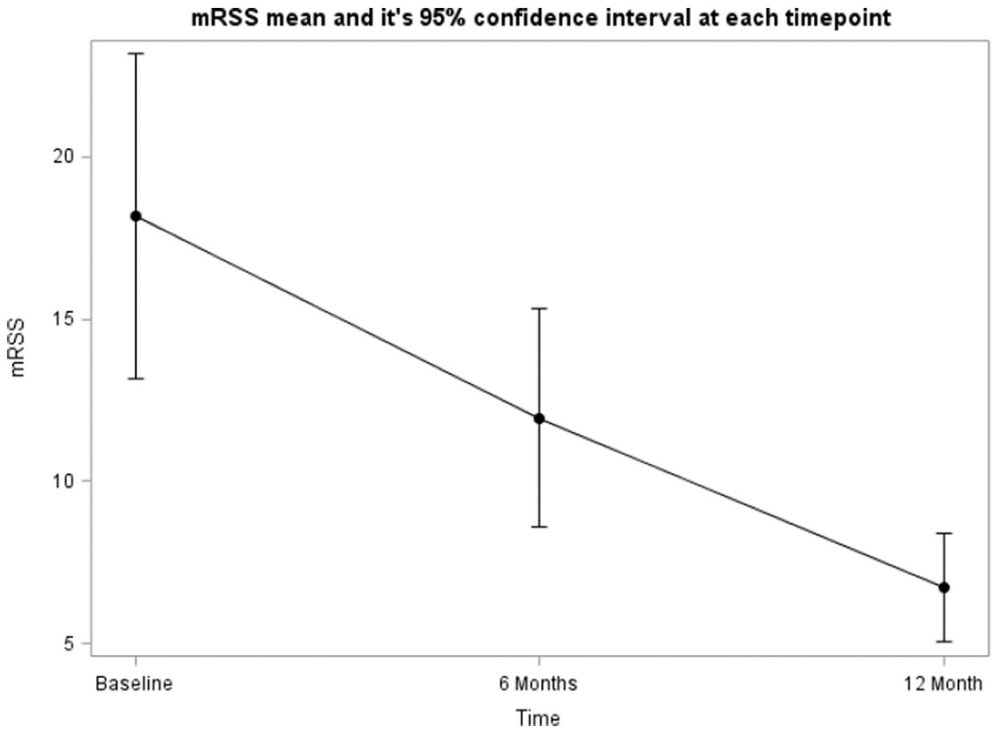

Fig. 2. mRSS mean and it's 95% confidence iterval at each timepoint.

follow-up, a statistically significant reduction of mRSS (average value of -6.61 ± 5.2, $p < 0.0001$) was achieved, reaching a significant stabilization after 12-months (-11.45 ± 9.63, $p < 0.0001$). At 12 months, still a significant reduction in comparison to 6 months ($p < 0.0002$) was observed (Table 2 and Fig. 3).

In 4 patients where at baseline mRSS was low (2; 2; 4; 5) IVIG were chosen because of refractory other organ involvement which was stabilised after the treatment. Two patients with joint pain and GI involvement showed only the amelioration of joint symptoms, while the other 2 were treated mainly for myositis with complete remission. In these patients the low mRSS did not show any progression during the period of observation, thus suggesting a stabilization.

In our patients, because of missing results about lung involvement did not allow any significant analysis. It is to be remarked that only minor short term adverse events were experienced (hypotension, nausea and dizziness).

4. Discussion

The data obtained from the SLR confirm that IVIG are a safe and efficient therapeutic tool for the control of skin involvement in SSc. Moreover, in our patients this therapeutic regimen has allowed a significant amelioration of the skin involvement after 24 and 48 weeks evaluation. These results are in line with those reported in the body of the literature, and emphasize the effectiveness of IVIG therapy, especially on skin involvement.

The SLR has identified some seminal papers that have clarified the regimen of IVIG infusion in SSc. In the study of Takehara et al. [30], been provided the evidence that a single administration of low dose of IVIG (0,4, g/Kg/month) is often insufficient to achieve a satisfactory result on skin thickness has been provided. In fact, IVIG became efficient at the second administration with a significant improvement of mRSS, with a change in the values of -8.3 ± 1.0 [30]. Thus, the authors suggested the choice of a multiple cycles regimen to obtain a significant effect of IVIG on skin thickness. It is worth of notice that in our cohort of patients, repeated cycles of IVIG have shown an interesting effect on skin involvement along other works that employed 6 to 8 cycles. The paper of Poelman et al. [29] has further strengthened the recommendation to use multiple cycles [29] because he observed a meaningful decrease of mRSS ($p < 0.0001$) at 6, 12,18 months and 24 months [29]. Also Asano et al. [34] and Kudo et al. [20] have also obtained satisfactory results on skin thickness after the first cycle.

The analysis of the literature clearly shows that the dose that allowed the largest number of improvements was 2 g/kg/month (instead of 0.4 g/kg/month, which was considered a low dose). However, still remains to be defined the length of the administration as it is not yet clear for how long the treatment should last. This is an important issue which needs to be elucidated as soon as possible and likely guidelines for the use of IVIG in SSc should be provided urgently to allow physicians to adopt in practice the best treatment schedule.

Table 2
mRSS variation from baseline to 6 and 12 months evaluation.

Variation mRSS								
Parameter	Difference estimate	Mean	SD	Test	P-value	Q1	Median	Q3
d06_mRSS	−6.61 (−8.86 to −4.36)	−6.61	5.21	Student *t*-test	<0.0001	−11.00	−5.00	−2.00
d012_mRSS	−11.45 (−15.72 to −7.18)	−11.45	9.63	Student *t*-test	<0.0001	−19.00	−10.50	−2.00
d6-12_mRSS	−5 [−8–0]	−5.05	4.88	Rank on sign	0.0002	−8.00	−5.00	0.00

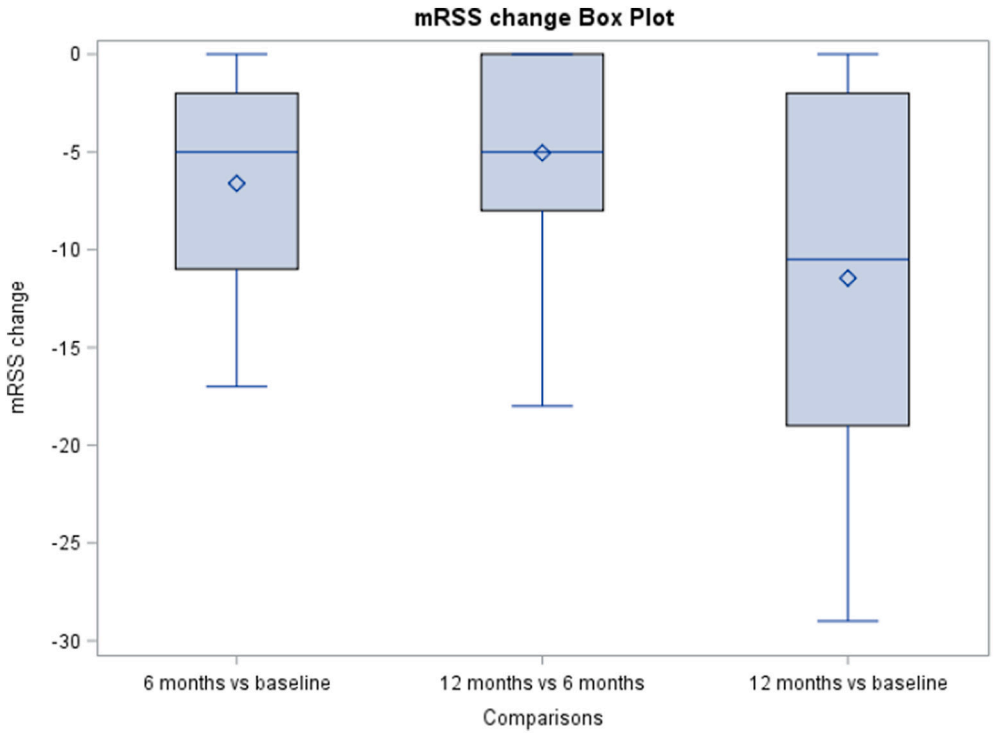

Fig. 3. mRSS change box plot.

In few studies and in our cohort, minor adverse events were reported in conjunction during IVIG infusion (vomit, dizziness etc). However, in 2 papers, severe adverse effects were reported (thromboembolic events, aseptic meningitis). The correlation is with the high doses of therapy and thromboembolism was the main worrisome report which merits a significant attention [35]. It should be said also that this kind of adverse event has been reported more than a decade ago and very likely the better preparation of IVIG has contributed to minimize today this problem.

In summary, from the global SLR (106 results), only 17 papers were identified after the separation of the clinical cases from the studies. In total, the number of treated patients was 183, and the organs mainly involved were gastrointestinal, skin, joint and cardiovascular systems. Only in one case, plasmapheresis was also associated. All papers reported significant improvements in the symptoms observed, although the organs which certainly get the greatest benefit from this therapy are the skin and the gastrointestinal system. A specific mention should be made for the cases of myositis which also significantly improved, as already well known from the literature [16,17] In addition, the best benefits have been obtained at high dosage (2 g/Kg/month), although repeated infusions of low doses of IVIG also brought improvement. Generally, the strength of the works was undermined by the lack of control cases or by the low number of patients involved.

It is well known that IVIG can prevent the development of infections, and for its immunomodulatory and anti-inflammatory effects. Some systemic autoimmune diseases may benefit from IVIG therapy, finding a variable efficacy depending on the clinical condition and the therapeutic protocol used. In our cohort of patients, IVIG therapy has been chosen due to the failure of standard of care, The treatment led to a statistically significant improvement of mRSS in 19 patients ($p < 0.0001$), still achieving a further, but milder improvement, in 20 patients at 12 months. For 4 patients with a low mRSS at baseline there was no significant improvement as they remained always stable at follow ups, possibly suggesting as a stabilization of skin involvement. In our patients, no severe adverse reactions to treatment were observed.

Our study on patients derived from real life has two main limits that are the small number of patients and the absence of a control group. On the other hand, the strong point is the fact that this experience derives from real life and the comparison inside the group may confirm the preliminary evidence that IVIG might be helpful in those patients that are refractory to standard of care therapies. Since new biological immunomodulatory and synthetic targeted therapies are emerging in this field, the use of IVIG still remains limited. However, in severe cases IVIG can be a valid rescue choice in patients intolerant or refractory to first-line therapies. Today, the high cost of IVIG treatment and their worldwide shortage represent a significant limit to their use in everyday practice.

In the future, double blind placebo controlled studies with larger number of patients are warranted to fully understand and to definitively confirm the efficacy of IVIG in SSc. Also therapeutic guidelines for IVIG use are awaited. Indeed, it may also be interesting to consider the possible combination of IVIG with other immunosuppressive or anti-proliferative drugs.

Declaration of Competing Interest

None.

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Corrigendum to "Intravenous immunoglobulins reduce skin thickness in systemic sclerosis: evidence from Systematic Literature Review and from real life experience" [Autoimmunity Reviews, Volume 20, Issue 12, December 2021, 102981]

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