Immunol Res (2015) 61:326–337
DOI 10.1007/s12026-014-8615-z

INTERPRETIVE SYNTHESIS REVIEW ARTICLE

Intravenous immunoglobulins (IVIG) in systemic sclerosis: a challenging yet promising future

Luca Cantarini · Donato Rigante · Antonio Vitale · Salvatore Napodano · Lazaros I. Sakkas · Dimitrios P. Bogdanos · Yehuda Shoenfeld

Published online: 31 December 2014

Abstract The etiology and pathogenesis of systemic sclerosis are still largely unknown, but a variety of humoral and cellular autoimmune phenomena have been documented. In addition, the rarity of the disease, the broad spectrum of clinical manifestations, and the relevant risk of severe complications as well as the highly variable disease course render its management a major challenge. Some immunomodulatory agents have been used, but no single agent has given a convincing proof of effectiveness, and treatment has remained largely symptomatic through recent years. Novel therapies are currently being tested and may have the potential of modifying the disease process and overall clinical outcome. Efficacy of intravenous immunoglobulins (IVIG) in different regimens (1–2 g/kg of body weight, administered over 2–5 consecutive days) has been described in a limited number of trials and small case series, showing benefits in skin, articular, and lung interstitial disease symptoms. However, studies on IVIG in systemic sclerosis still remain few, and further randomized controlled trials should be undertaken to assess their clinical effectiveness or define the optimal dosage and times of administration.

Keywords Systemic sclerosis · Intravenous immunoglobulins · Therapy · Autoimmunity

Luca Cantarini and Donato Rigante have equally contributed to this manuscript.

L. Cantarini · A. Vitale
Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy

L. Cantarini (✉)
Rheumatology Unit, Policlinico "Le Scotte", University of Siena, Viale Bracci 1, 53100 Siena, Italy
e-mail: cantariniluca@hotmail.com

D. Rigante · S. Napodano
Institute of Pediatrics, Università Cattolica Sacro Cuore, Rome, Italy

L. I. Sakkas · D. P. Bogdanos
Department of Rheumatology, School of Health Sciences, University of Thessaly, Larissa, Greece

D. P. Bogdanos
Division of Transplantation Immunology and Mucosal Biology, King's College London, London, UK

Y. Shoenfeld
The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel

Y. Shoenfeld
Sackler Faculty of Medicine, Tel Aviv University, Tel-Hashomer, Israel

Introduction

The hallmarks of systemic sclerosis (SSc) are progressive skin fibrosis, obliteration of the microvasculature, and exaggerated extracellular matrix deposition. This latter affects internal viscera and results in tissue architecture distortion with progressive loss of organ function. The pathophysiology of SSc is not fully understood. However, pathogenetic mechanism in SSc involves multiple humoral and cellular immunity abnormalities mainly resulting in the production of specific autoantibodies and profibrotic cytokines [1, 2]. Genetic factors are unlikely to play a major role in the development of this disease, as the concordance rate of the disease in monozygotic twins is low and comparable to that in dizygotic twins [3]. Environmental

factors most probably participate in the loss of immunological tolerance to SSc-specific autoantigens and the induction of the disease. In particular, infections can elicit molecular mimicry, endothelial cell damage, and superantigen immune activation leading to disease progression [4–6]. Several non-infectious environmental agents have also been implicated in the development of the disease [7–20]. In addition, epigenetic changes, such as DNA methylation, and micro-RNAs have been described in SSc [21, 22]. This review will briefly focus the potential role of intravenous immunoglobulins (IVIG) as an alternative treatment regimen in a subset of patients with SSc resistant to conventional therapeutic approaches.

Recognizing and treating a complex disease

Skin, lungs, kidneys, gastrointestinal tract, and vessels are frequently involved in SSc [23]. Skin becomes thickened and may have telangiectasia. Based on skin involvement, the disease is divided into limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) forms [24, 25]. Raynaud's phenomenon is a common and early clinical manifestation and confers a risk of digital ulcers [26–28]. Gastrointestinal motility impairment is the second most frequent SSc manifestation after skin involvement, affecting almost any part of the gastrointestinal tube, but especially the esophagus [29]. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) represent the leading causes of dcSSc-related deaths and are associated with anti-Scl70 antibody positivity [30]. ILD usually occurs more severely during the first 3–4 years of the disease and is more frequent in patients with early disease onset [31], while PAH usually occurs in females as a late complication of lcSSc [32]. A less frequent manifestation, scleroderma renal crisis (SRC), presents with accelerated arterial hypertension and/or rapidly progressive oliguric renal failure, and/or micro-angiopathic hemolytic anemia. SRC is a severe renal manifestation, and it is associated with the presence of anti-RNA polymerase III autoantibodies, large joint contractures at baseline, and a moderate-to-high dose corticosteroid administration [33, 34]. SRC usually occurs in the first 4 years of the disease [35]. Cardiac involvement is often overlooked, though identified in almost all patients when carefully searched: cardiac involvement can be revealed by rhythm abnormalities, pericardial effusion, transient ischemia, and myocardial fibrosis with or without heart failure [36].

A number of regimens have been introduced in SSc, mostly based on the specific type of organ and tissues involved, often without efficacy. Corticosteroids are part of the therapeutic strategy in the management of dcSSc, ILD, and cardiac involvement. However, SRC can represent a troublesome corticosteroid complication, mostly if nephrotoxic agents are concomitantly used [37]. Calcium channel blockers are the cornerstone of therapy for Raynaud's phenomenon and digital ulcers [38], endothelin receptor antagonists may prevent new digital ulcers [39], and phosphodiesterase type-5 inhibitors or prostacyclin analogs reduce Raynaud's attack frequency or promote digital ulcer healing [40, 41]. Many conventional immunomodulatory drugs acting by inhibiting activation or reducing proliferation of lymphocytes, namely methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil, have been used both to control symptoms and to retard or arrest the progression of SSc with different organ involvement. Their efficacy is largely variable [42]. Among biologic therapies, rituximab appears the most promising agent and shows benefit on skin SSc thickness and may stabilize or even improve lung function [43]. The anti-interleukin-6 agent tocilizumab and the selective co-stimulation modulator/T cell inhibitor abatacept have shown a possible therapeutic effect in refractory SSc-related polyarthritis and myopathy [44]. After many unsuccessful anti-fibrotic treatments and even hematopoietic stem cell transplantation, often associated by high mortality rates [45, 46], treatment options for SSc have been realistically restricted to IVIG.

The intravenous immunoglobulins

IVIG is a human polyspecific IgG (presented as monomeric or multimeric forms, Fig. 1) derived from the plasma of thousands of healthy blood donors (3,000–60,000) and has been increasingly used during the last decades for an increasing number of systemic immune-mediated and heterogeneous inflammatory diseases. At first, IVIG represented the standard therapy for patients with immune deficiencies, but subsequently, studies revealed that IgG-Fc confers protection against several clinical conditions, ranging from transplantation to autoimmunity. In particular, disorders effectively treated with IVIG include hematological disorders, such as idiopathic thrombocytopenic purpura; neuro-immunological diseases, such as Guillain-Barré syndrome, acute myasthenia gravis, and chronic idiopathic demyelinating polyneuropathy; different dermatoses, such as pemphigus vulgaris, pemphigoid, toxic epidermal necrolysis, and Stevens-Johnson syndrome; and rheumatologic immune-mediated diseases, such as Kawasaki syndrome (in which IVIG is the standard of care treatment), dermatomyositis, and anti-neutrophil cytoplasmic antibody-related vasculitides [47–50].

The host of disorders treatable with IVIG suggests the existence of multiple non-exclusive mechanisms of action (Table 1) [51–60]. To date, IVIGs' beneficial effects are

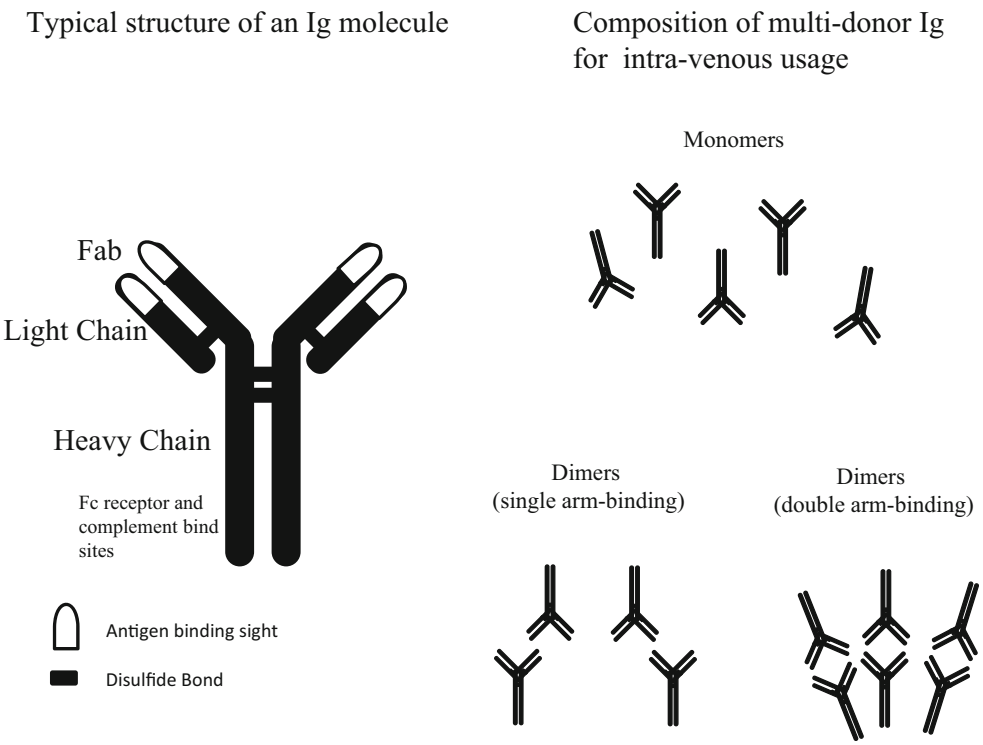

Fig. 1 IgG can be monomeric or can form multimers (mainly dimers but also aggregates). IVIG infusion can lead to the formation of IgG dimers with donor or host IgG. IgG monomers can interact with either FcγRI or FcRn; multimeric IgG can interact with low affinity FcγRs

Table 1 Selected mechanisms of action of IVIG in human disease and experimental models of autoimmune diseases (reviewed by [55])

Mechanism of action	Paradigms of autoimmune disease settings	References	General comments
Fc	Immunothrombocytopenia (ITP), murine nephrotoxic nephritis, murine arthritis, experimental autoimmune encephalomyelitis	[51–53]	Fc fragment of IgG is the most important for IVIG's immunomodulatory actions; Fc fragments are able to ameliorate (ITP).; IVIG depleted of anti-idiotypic antibodies or IgG-Fc fragments confers protection from autoantibody-dependent ITP, arthritis, and antibody-mediated lung injury
$F(ab')_2$	Experimental autoimmune encephalomyelitis	[53, 54]	The role of $F(ab')_2$ is debatable. Recent data suggested that IVIg or $F(ab')_2$ fragments decrease the sphingosine-1 phosphate receptor on CD4 cells, leading to their sequestration in the draining lymph nodes and their decreased infiltration into the CNS
FcγRIIB	Murine model of immune thrombocytopenia	[55]	FcγRIIB-deficient mice or mice with blocked FcγRIIB function are unresponsive to IVIG in murine models of ITP
FcRn	Murine bullous pemphigoid	[56]	The involvement of neonatal Fc receptor (FcRn) in IVIG's action is rather complex. FcRn-deficient mice are resistant to autoantibody-mediated induction of skin blisters in the bullous pemphigoid model. It is possible that IVIG preparations compete with pathogenic autoantibodies for FcRn binding.
SIGNR1	Murine arthritis, murine ITP	[57]	Splenectomy, loss of positive SIGN-R1 (specific ICAM-3 grabbing non-integrin-related 1), cells or genetic deletion of SIGN-R1 abrogate the anti-inflammatory activity of IVIG or sialylated Fc fragments.
Glycosylation		[58–60]	Patients with Crohn's disease, ulcerative colitis, and rheumatoid arthritis have increased levels of IgG glycoforms lacking terminal sialic acid and galactose residues

not yet fully understood, though their immunoregulatory activity seems to be related mainly to the Fc part of the IgG [51, 55] (Fig. 2). They are also known to induce modifications both in the innate and acquired immune systems by acting on many immune cell types. In particular, IVIG effect has been associated but not limited to (i) an increase in the number and suppressive function of regulatory T cells [61, 62]; (ii) a modulation in the proliferation and differentiation of B cells and their antibody production by increasing activated B cells, stimulating the secretion of natural antibodies and neutralization anti-cytokine antibodies (Fig. 3) and interfering with autoantibody production or reducing the capability of B cells to present antigens [63, 64]; (iii) dendritic cell inhibition and differentiation from monocytes [65]; (iv) suppression of activated peripheral blood monocytes and decreased macrophage activation or degranulation [66, 67]; (v) modulation of pro/anti-inflammatory cytokine secretion, such as reduction in tumor necrosis factor (TNF)-α production and increase in soluble TNF receptor, and interleukin (IL)-1 receptor antagonist [68]; and (vi) up-regulation of cell surface receptors, including Toll-like receptor family and receptors actively involved in the phagocytosis, antigen presentation, and cell-to-cell adhesion [52, 55, 69]. In addition, genetic and functional variations in Fc receptors as well as the differential IgG-Fc glycosylation patterns could play a role in modulating an inflammatory response. Indeed, sialic acid-enriched IVIG preparations have shown a greater anti-inflammatory activity, while the removal of the terminal sialic acid has abrogated the IVIG protective effect [58, 70].

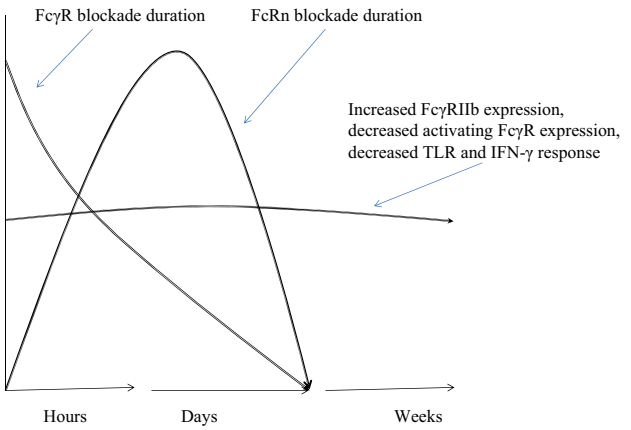

Fig. 2 There are most likely distinct Fc receptor-related mechanism of actions of IVIG and the kinetics of these mechanisms largely vary over time. Competitive interference of IVIG with FcγR binding does not last for long, while FcRn-dependent clearance is lasting over several days. More sustainable is expected to be the induction of ITAM-mediated anti-inflammatory/immunosuppressive action of IVIG which includes increased expression of FcγRIIb, diminished expression of FcγR, and decreased expression of TLR and proactive cytokines such as IFNγ

Although dosages and timing of administration are not defined, the immunomodulating IVIG action generally requires the use of several pulses, each consisting of 1–2 g/kg of body weight, administered over 2–5 consecutive days [71]. The high dosages needed, along with the increasing use of IVIG worldwide, have brought about shortages in IVIG supply and increased their cost. For these reasons, the development of new bioengineered substitutes for IVIG has become mandatory. Current efforts are based on IVIG putative working mechanisms and include recombinant IVIG with hyper-sialylated IgG [70]. Adverse reactions are usually sub-grouped to four categories; (a) related to underlying infection; (b) rate related; (c) ron-rate related; and (d) related to high-dose treatment. The incidence of serious adverse reactions remains rather small and includes arterial thrombosis, severe anaphylactic reactions, aseptic meningitis, and renal tubular crisis. Most adverse effects are mild and non-anaphylactic, and limited to nausea, rhinitis, asthma, chills, low-grade fever, myalgia, and migraine headache [48, 72]. The variables potentially affecting the risk and intensity of adverse events include patient's age, cardiovascular or renal disease, dyslipidemia, diabetes, IgA deficiency with anti-IgA antibodies, IVIG dose used, specific formulations, immobilization, and eventual excipients [73, 74].

Management of systemic scleroderma with intravenous immunoglobulins

During the last years, an increasing interest has been paid to IVIG as an alternative therapy for SSc. Indeed, experimental data, controlled clinical trials, one randomized double-blind placebo-controlled trial, and several case reports have shown that IVIG may have a beneficial effect on multiple clinical manifestations of SSc, such as skin fibrosis, calcinosis, joint involvement, and even SSc-related ILD.

Various independent papers have reported on IVIG administration in patients with SSc, and Table 2 summarizes a list of all published articles reporting data on the treatment with IVIG. Table 3 summarizes the main advantages and disadvantages of IVIGs.

In 1990, Bodemer et al. firstly reported IVIG's beneficial effects in sclerodermatomyositis [75]. Few years later, IVIGs were administered in an 11-year-old boy with a pansclerotic morphea, who showed an improvement in his leg ulcers [76]. In 2000, three patients with rapidly progressive SSc, mainly affecting the skin, were treated with high-dose IVIG: All three patients exhibited a substantial improvement in skin thickness compared with baseline skin thickness. However, one patient received only three monthly courses after which he developed renal failure and

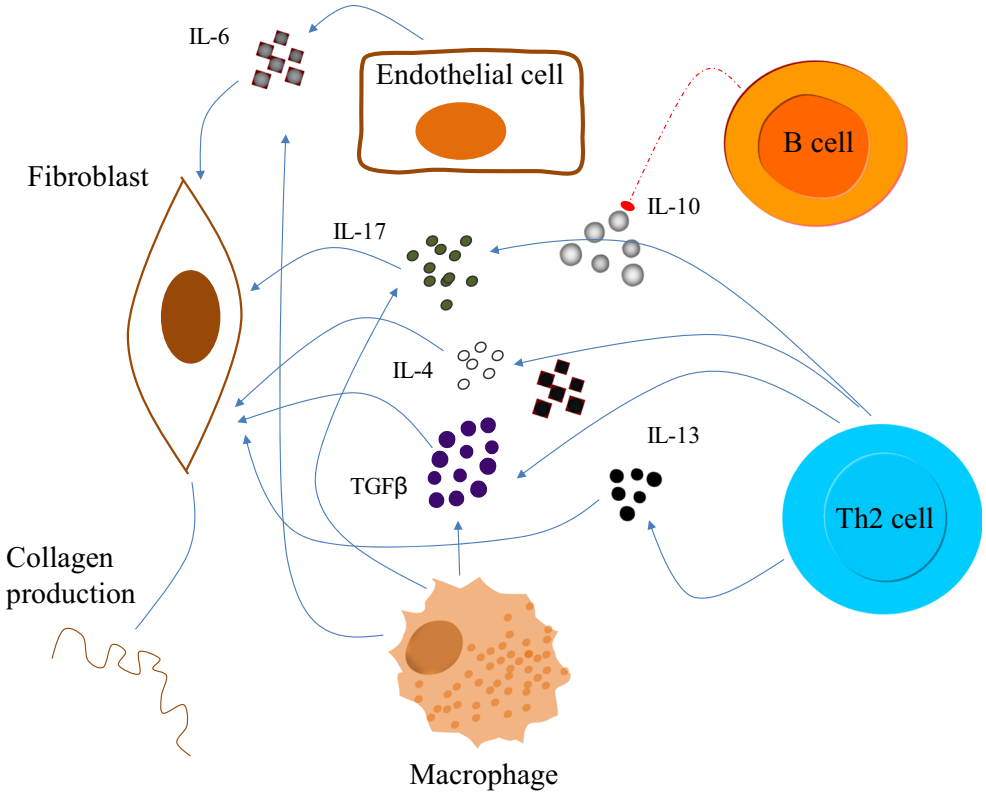

Fig. 3 IVIG involvement in cellular–cytokine interactions involved in the pathogenesis of SSc. Several cytokines induced by macrophages, T cells, and B cells as well as endothelial cells are involved in the fibroblast-induced collagen induction. In a hypothetical scenario, IVIG leads to cytokine neutralization mediated by IVIG, and this has a negative impact in the maintenance of fibrogenesis by inducing extracellular matrix degradation or by the inhibition of collagen production from fibroblasts. The reduction of pro-inflammatory cytokine production and the enhancement of anti-inflammatory cytokine production are only two of the several actions of IVIG. IVIG can stimulate B cells to produce IL-10 exerting a B regulatory function. Also, IVIG has an apoptotic effect on autoreactive B cells, neutralizes factors involved in autoreactive B cell survival, augments the inhibitory effect of FcγRIIB, diminishes B cell proliferation, and immunoregulates autoantibody induction

later died of sepsis [77]. In 2004, an open-label study on ten patients with dcSSc and five subjects with lcSSc treated with monthly IVIG infusions found that the mean degree of skin involvement evaluated with the modified Rodnan skin score decreased by 35 % during the time of the study, while a significant improvement in patients' well-being and quality of life was identified by means of a decrease in the Health Assessment Questionnaire (HAQ) score. Notably, although differences did not reach statistical significance, patients with a longer disease duration showed a more pronounced Rodnan skin score improvement when compared with SSc patients with a shorter disease duration (44 vs. 21 %) [78]. Another 60-year-old Japanese woman with SSc successfully treated with IVIG was reported one year later: The modified Rodnan skin score and histological skin biopsies performed before and 4 weeks after IVIG administration showed that skin thickness was dramatically reduced [79]. Similarly, in 2007, a pilot study conducted on seven women with SSc showed a significant improvement in six patients. In particular, a reduction in the modified Rodnan skin score by 28 % was identified after 6 months of IVIG therapy. Furthermore, joint pain and tenderness measured with the visual analogue scale also improved significantly, leading to recovery of hand function, decrease in the mean number of swollen joints (from 10 to 7) and tender joints (from 19 to 10), and overall improvement in the quality of life [80]. In the same year, Ihn et al. studied five patients with SSc undergoing IVIG infusions (400 mg/kg/daily for five consecutive days) and followed for 34–70 weeks thereafter: On the basis of the modified Rodnan skin thickness scoring, all five patients showed marked improvement in skin thickness from 2 weeks after infusion to the end of the trial. These findings were also corroborated by histological assessment performed in two of those. In addition, a digital tip ulcer in one patient healed during the trial. Mild adverse effects were recorded during the observation period including headache in one patient and nausea in another [81]. Interestingly, Schanz et al. reported a 56-year-old woman with CREST syndrome, a variant of systemic sclerosis, who

Table 2 List of published articles reporting data on the treatment with intravenous immunoglobulins in patients with systemic scleroderma

Publication (reference)	Number of patients	Condition diagnosed	IVIG dosage	Times of administration	Treatment duration	Clinical results reported	Adverse events
Case report [75]	1	SSc-dermatomyositis overlap	400 mg/kg/day for 5 days every 10 days; after 2 months, 1 g/day for 2 days monthly	Monthly	6-month follow-up reported	Myositis improvement; scleroderma-like infiltration improved; calcification regressed; digital necrosis areas healed; lung function test improved	Not cited
Case report [76]	1	Pansclerotic morphea complicated by leg ulcers	5 g/day for 5 days	Monthly	More than one year	Amelioration of ulcers	None
Case report [77]	3	SSc	2 g/kg on a 5-day schedule	Monthly	6 cycles (patients 1 and 2); 3 cycles (patient 3)	Rodnan skin score improvement; no effect on the restrictive lung disease was noted (patient 1)	Patient 1 and 2: none; patient 3: fever, cough, hypertension occurring after the third IVIG infusion, kidney deterioration, and pulmonary edema occurred a few weeks after IVIG withdrawal (a few weeks later, the patient died from sepsis)
Open-label study [78]	15	10 dcSSc patients and 5 lcSSc patients	2 mg/kg over a 5-day period for each course	Monthly	6 cycles (11 patients), 4 cycles (3 patients), 1 cycle (1 patient)	Modified Rodnan skin score; HAQ improvement	Not cited
Case report [79]	1	dcSSc	400 mg/kg daily for 5 consecutive days	–	–	Thickness was dramatically reduced at modified Rodnan skin score and bioptic evaluations	None
Pilot study [80]	7	5 lcSSc patients; 2 dcSSC patients	2 g/kg during 4 days	Monthly	6 cycles	Joint pain and tenderness amelioration; modified Rodnan skin score and HAQ improvement; functionality improvement in 6/7 patients	None
Open-label trial [81]	5	dcSSc	400 mg/kg for 5 consecutive days	–	1 cycle	Modified Rodnan skin score and biopsies were markedly improved	Headache in one patient, nausea in another
Case report [82]	1	CREST syndrome	2 g/d in a 4-day protocol	Monthly	5 cycles	Pain and inflammation linked to dystrophic calcifications disappeared; Rodnan skin score improved	None
Case report [83]	1	dcSSc	15 g/monthly; plasmapheresis was combined	Monthly for one year, then every 3 months	Several years	Marked improvement in the skin score and in swollen and tender joint counts; decline of disease progression	Not cited

Table 2 continued

Publication (reference)	Number of patients	Condition diagnosed	IVIG dosage	Times of administration	Treatment duration	Clinical results reported	Adverse events
Open-label trial [84]	1/17 patients suffered from SSc	SSc	400 mg/kg/day for 5 days	Monthly for 6 months, then every 2–3 months	8 cycles	The patient was partially responsive (a more accurate clinical description was not available)	Not cited
Randomized, double-blind, placebo-controlled trial [85]	63	dcSSc	400 mg/kg/day for 5 consecutive days	1 or 2 single courses (400 mg/kg/day for 5 consecutive days)	–	After a single IVIG infusion, no significant differences were identified among groups; repeated administration of IVIG determined a significant improvement in the MRSS	Frequency of AE was not different between IVIG and placebo groups
Case report [86]	1	SSc with myositis	2 mg/kg/month combined with azathioprine (150 mg/day)	Monthly	6 cycles reported	Full recovery of lung function; muscle strength recovery	AE were not cited

HAQ Health Assessment Questionnaire, *IVIG* intravenous immunoglobulins, *SSc* systemic scleroderma, *dcSSc* diffuse cutaneous systemic scleroderma, *lcSSc* limited cutaneous systemic scleroderma, *MRSS* modified Rodnan skin thickness score, *AE* adverse events

Table 3 Advantages and disadvantages of IVIG in autoimmune diseases

Advantages
Proven clinical utility in various autoimmune diseases
Well tolerated by the great majority of the patients
Adverse reactions infrequent. Severe adverse reactions rare.
Disadvantages
Proven clinical utility is seen in a relatively small percentage of autoimmune diseases
High cost
Mild adverse reactions (such as headache, nausea, and low-grade fever) are relatively frequent
Serious adverse reactions maybe fatal
Great variability in IgG levels during dosing can lead to adverse effects at peaking, as well as during low troughs
Requires venous access
Requires trained personnel

mainly suffered from debilitating dystrophic calcium deposits refractory to several therapies and causing inflammation, pain, and swelling of the index finger of her left hand: After two IVIG courses, patient's pain and inflammation subsided, and after further three more courses, she was completely symptom-free. Also, the Rodnan skin score improved after this treatment [82].

One year later, Szekanecz et al. reported a male patient diagnosed with dcSSc resistant to conventional therapy, who underwent a 12-month treatment with a combination of plasmapheresis performed every 2–3 months and IVIG on a monthly basis. That therapeutic approach proved to slow down the rapid progression of the disease. Moreover, a marked improvement in the skin score, as well as in swollen and tender joint counts, was recorded. The clinical improvement was sustained during the following years with sessions of plasmapheresis and IVIG treatment every 3 months [83]. In 2012, Zandman-Goddard et al. administered IVIG to 17 patients with autoimmune disorders, including a 34-year-old patient with SSc, who was described as partially responsive [84]. In 2013, Takehara et al. investigated the efficacy of IVIG for skin sclerosis in a large cohort of 63 patients with dcSSc. This study was a randomized, double-blind, placebo-controlled multicenter trial, and the design arms included administration of IVIG or placebo for 5 consecutive days in a single course. Twelve weeks after IVIG/placebo administration or at discontinuation (primary endpoint), patients with at least a 5-point improvement in the modified Rodnan skin score were continuously observed. Those patients belonging to IVIG or placebo groups with a less remarkable amelioration were administered with IVIG (readministration study). At primary endpoint, no significant differences were found among IVIG/placebo groups with regard to modified

Rodnan skin score. Notably, a significant improvement was obtained when patients receiving IVIG twice were compared with patients receiving IVIG for the first time [85]. More recently, Mauhin et al. described a 53-year-old woman suffering from SSc, myositis, and early-stage ILD. The regression of ground-glass opacities and septal thickening on chest high-resolution computed tomography with full recovery of lung function after IVIG and azathioprine administration suggested that IVIG therapy can also contribute to reduction of alveolar inflammation and fibrosis [86].

Mode of action of IVIG in experimental systemic scleroderma

To date, the mechanisms of action by which IVIG might improve fibrosis in SSc remain unclear. However, a number of possible explanations regarding the potential actions of IVIG have been suggested. Blank et al. [87] demonstrated that IVIG decreases collagen deposition and type I collagen expression in tight skin mice, a murine model of a scleroderma-like disease. Notably, the reduction in skin fibrosis after IVIG was accompanied by decreased secretion of the profibrotic cytokines IL-4 and transforming growth factor (TGF)-β1 by splenocytes. Similarly, Kajii et al. investigated IVIG effects on fibrosis in a murine model of bleomycin-induced scleroderma and found that IVIG drastically ameliorated the dermal thickening in bleomycin-injected mice. In addition, TGF-β mRNA levels in lesional skin of mice, as well as monocyte chemoattractant protein (MCP-1) levels determined by ELISA, were found to be up-regulated in bleomycin-treated mice and subsequently suppressed after IVIG treatment. Furthermore, immunohistochemical evaluation of cellular infiltration in the dermal layer during early stages of bleomycin-induced disease showed that macrophages were the most abundant infiltrated cells. It was finally suggested that IVIG might inhibit macrophage recruitment to the fibrotic sites by down-regulating MCP-1 and TGF-β production [88].

The role of cytokines in IVIG-treated systemic scleroderma

According to Kudo et al., the mechanism by which IVIG treatment exerts its anti-fibrotic effect may involve Th1 cytokine expression [89]. That study has measured serum levels of interferon (IFN)-γ and IL-12 before and after IVIG infusions or placebo administration and found their concentrations increased in the IVIG group compared with the placebo group, where no changes were noted. This result was confirmed by immunostaining of skin biopsy specimens before and after the first IVIG administration or placebo. Furthermore, mRNA expression of IFN-γ and IL-12 was significantly increased by IVIG treatment in SSc skin tissue [89]. Of interest, previous studies have reported decreased levels of an IFN-γ and IL-12 in SSc patients [90, 91]. Nevertheless, other mechanisms could also be involved: IVIG can bind directly to TGF-β [92] and down-regulate T cell expression, resulting in decreased fibroblast TGF-β production. It can also mediate its effect by inhibiting the complement activation, and through the presence of anti-fibroblast antibodies within IVIG preparation [93, 94]. New randomized trials on SSc with IVIG are under way [clinicalTrials.gov]. Hence, a double-blind, randomized, placebo-controlled study (NCT01785056) is recruiting patients to assess the safety and efficacy of intravenous immunoglobulin in patients with SSc. The study will last 12 months and is expected to recruit approximately 24 subjects. The study will assess the effects of IVIG on skin involvement in patients with scleroderma. The study is an investigator-initiated study at Georgetown University Hospital and Johns Hopkins Hospital.

All these varied experiences suggest that IVIG should be included as a potential alternative therapeutic option of SSc, particularly if skin fibrosis and joint fibrotic involvement exist. It is of note that IVIG administration is allowed during pregnancy [95], and indeed, although significant amounts of immunoglobulins cross the placenta, no adverse effects on both fetus and neonate have ever been reported [96, 97]. The increased cost of IVIG compared with other conventional treatment is an obstacle. There is no doubt that a patient-centered cost-benefit analysis of IVIG administration in SSc will be needed to estimate whether treatment with this regimen is likely to result in lower cost and better outcome.

Conclusions

The remarkable complexity of SSc at a clinical level is mirrored by the large amount of potential treatment strategies available to control the protean signs of this disabling disorder. Management decisions are centered on both the degree of disease activity and the specific organ involvement, without considering the overall disease biologic process. Treatment with IVIG is proving to be an effective option on skin fibrosis and joint manifestations of SSc. To date, however, due to the rarity of SSc, studies on the effects of IVIG remain relatively few, mainly represented by case reports or limited cohorts of patients. For these reasons, further multicenter randomized controlled trials are needed in order to evaluate the real role of IVIG in SSc and identify optimal dose or times of administration.

Take-home messages

- Systemic scleroderma is a generalized autoimmune disorder characterized by extensive accumulation of collagen, leading to progressive fibrosis which might involve skin and major organs with significant morbidity and diminished overall quality of life.
- The wide variability of clinical manifestations is often faced with a symptomatic organ-specific management of the disease without looking at the specific control of its pathogenesis.
- Increasing interest has been paid to treatment with intravenous immunoglobulins as an alternative therapy in multi-resistant patients with systemic scleroderma.
- Possible troublesome adverse reactions during treatment with intravenous immunoglobulins along with shortages in supply and high costs should prompt physicians to not use this therapeutic option indiscriminately.
- Different experiences with intravenous immunoglobulins in patients with systemic scleroderma are encouraging in terms of skin, articular, and lung interstitial disease symptoms, though the correct evaluation of these studies remains arduous.
- Data actually available on intravenous immunoglobulins in systemic scleroderma are still limited, and further multicenter randomized controlled trials should be undertaken to assess their clinical effectiveness or define their optimal dosage and times of administration.

Conflict of interest None.

References

1. Mehra S, Walker J, Patterson K, Fritzler MJ. Autoantibodies in systemic sclerosis. Autoimmun Rev. 2013;12:340–54.
2. Sakkas LI, Chikanza IC, Platsoucas CD. Mechanisms of disease: the role of immune cells in the pathogenesis of systemic sclerosis. Nat Clin Pract Rheumatol. 2006;2:679–85.
3. Feghali-Bostwick C, Medsger TA Jr, Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. Arthritis Rheum. 2003;48:1956–63.
4. Grossman C, Dovrish Z, Shoenfeld Y, Amital H. Do infections facilitate the emergence of systemic sclerosis? Autoimmun Rev. 2011;10:244–7.
5. Randone SB, Guiducci S, Matucci-Cerinic M. Systemic sclerosis and infections. Autoimmun Rev. 2008;8:36–40.
6. Lanteri A, Sobanski V, Langlois C, Lefèvre G, Hauspie C, Sanges S, Lambert M, Morell-Dubois S, Hatron PY, Hachulla E, Launay D, Dubucquoi S. Serum free light chains of immunoglobulins as biomarkers for systemic sclerosis characteristics, activity and severity. Autoimmun Rev. 2014. doi:10.1016/j.autrev.2014.07.003.
7. Trad S, Nosbaum A, Musset L, Ghillani-Dalbin P, Launay D, Costedoat-Chalumeau N, Saadoun D, Cabane J, Hachulla E, Hanslik T, Frances C. Systemic sclerosis and prevalence of monoclonal immunoglobulin. Autoimmun Rev. 2014. doi:10.1016/j.autrev.2014.08.016.
8. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev. 2014. doi:10.1016/j.autrev.2014.07.001.
9. Bernal-Bello D. García de Tena J, Simeón-Aznar C, Fonollosa-Pla V. Systemic sclerosis, breast cancer and calcium channel blockers: a new player on the scene? Autoimmun Rev. 2014;13:880–1.
10. Calixto OJ, Anaya JM. Socioeconomic status. The relationship with health and autoimmune diseases. Autoimmun Rev. 2014;13:641–54.
11. Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, Bravard P, Noël D, Cailleux AF, Weber J, Lagoutte P, Benichou J, Levesque H. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. Autoimmun Rev. 2014;13:151–6.
12. Elhai M, Avouac J, Kahan A, Allanore Y. Systemic sclerosis at the crossroad of polyautoimmunity. Autoimmun Rev. 2013;12:1052–7.
13. Osnes LT, Nakken B, Bodolay E, Szodoray P. Assessment of intracellular cytokines and regulatory cells in patients with autoimmune diseases and primary immunodeficiencies—novel tool for diagnostics and patient follow-up. Autoimmun Rev. 2013;12:967–71.
14. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun Rev. 2012;12:127–36.
15. Iaccarino L, Gatto M, Bettio S, Caso F, Rampudda M, Zen M, Ghirardello A, Punzi L, Doria A. Overlap connective tissue disease syndromes. Autoimmun Rev. 2013;12:363–73.
16. Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev. 2012;11:A502–14.
17. Lee TP, Chiang BL. Sex differences in spontaneous versus induced animal models of autoimmunity. Autoimmun Rev. 2012;11:A422–9.
18. Farhat SC, Silva CA, Orione MA, Campos LM, Sallum AM, Braga AL. Air pollution in autoimmune rheumatic diseases: a review. Autoimmun Rev. 2011;11:14–21.
19. Liakouli V, Cipriani P, Marrelli A, Alvaro S, Ruscitti P, Giacomelli R. Angiogenic cytokines and growth factors in systemic sclerosis. Autoimmun Rev. 2011;10:590–4.
20. Cipriani P, Marrelli A, Liakouli V, Di Benedetto P, Giacomelli R. Cellular players in angiogenesis during the course of systemic sclerosis. Autoimmun Rev. 2011;10:641–6.
21. Costenbader KH, Gay S, Alarcón-Riquelme ME, Iaccarino L, Doria A. Genes, epigenetic regulation and environmental factors: which is the most relevant in developing autoimmune diseases? Autoimmun Rev. 2012;11:604–9.
22. Jimenez SA, Piera-Velazquez S. Potential role of human-specific genes, human-specific microRNAs and human-specific non-coding regulatory RNAs in the pathogenesis of systemic sclerosis and Sjögren's syndrome. Autoimmun Rev. 2013;12:1046–51.
23. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev. 2010;9:A311–8.
24. Foti R, Leonardi R, Rondinone R, Di Gangi M, Leonetti C, Canova M, Doria A. Scleroderma-like disorders. Autoimmun Rev. 2008;7:331–9.
25. Careta MF, Leite Cda C, Cresta F, Albino J, Tsunami M, Romiti R. Prospective study to evaluate the clinical and radiological outcome of patients with scleroderma of the face. Autoimmun Rev. 2013;12:1064–9.
26. Prete M, Fatone MC, Favoino E, Perosa F. Raynaud's phenomenon: from molecular pathogenesis to therapy. Autoimmun Rev. 2014;13:655–67.

27. Galluccio F, Matucci-Cerinic M. Two faces of the same coin: Raynaud phenomenon and digital ulcers in systemic sclerosis. Autoimmun Rev. 2011;10:241–3.
28. Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. Autoimmun Rev. 2006;5:125–8.
29. Almeida I, Faria R, Vita P, Vasconcelos C. Systemic sclerosis refractory disease: from the skin to the heart. Autoimmun Rev. 2011;10:693–701.
30. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, Müller-Ladner U, Bocelli-Tyndall C, Matucci-Cerinic M. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66:754–63.
31. Plastiras SC, Karadimitrakis SP, Ziakas PD, Vlachoyiannopoulos PG, Moutsopoulos HM, Tzelepis GE. Scleroderma lung: initial forced vital capacity as predictor of pulmonary function decline. Arthritis Rheum. 2006;55:598–602.
32. Lambova S, Müller-Ladner U. Pulmonary arterial hypertension in systemic sclerosis. Autoimmun Rev. 2010;9:761–70.
33. Guiducci S, Giacomelli R, Cerinic MM. Vascular complications of scleroderma. Autoimmun Rev. 2007;6:520–3.
34. Steen VD. Scleroderma renal crisis. Rheum Dis Clin North Am. 2003;29:315–33.
35. Guillevin L, Bérezné A, Seror R, Teixeira L, Pourrat J, Mahr A, Hachulla E, Agard C, Cabane J, Vanhille P, Harle JR, Deleveaux I, Mouthon L. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. Rheumatology. 2012;51:460–7.
36. Hollan I, Meroni PL, Ahearn JM, Cohen Tervaert JW, Curran S, Goodyear CS, Hestad KA, Kahaleh B, Riggio M, Shields K, Wasko MC. Cardiovascular disease in autoimmune rheumatic diseases. Autoimmun Rev. 2013;12:1004–15.
37. Iudici M, van der Goes MC, Valentini G, Bijlsma JW. Glucocorticoids in systemic sclerosis: weighing the benefits and risks—a systematic review. Clin Exp Rheumatol. 2013;31:157–65.
38. Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. Arthritis Rheum. 2001;44:1841–7.
39. Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, Rich E, Carpentier P, Molitor J, Seibold JR, Hsu V, Guillevin L, Chatterjee S, Peter HH, Coppock J, Herrick A, Merkel PA, Simms R, Denton CP, Furst D, Nguyen N, Gaitonde M, Black C. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004;50:3985–93.
40. Fries R, Shariat K, von Wilmowsky H, Böhm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation. 2005;112:2980–5.
41. Wigley FM, Seibold JR, Wise RA, McCloskey DA, Dole WP. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. J Rheumatol. 1992;19:1407–14.
42. Herrick AL, Lunt M, Whidby N, Ennis H, Silman A, McHugh N, Denton CP. Observational study of treatment outcome in early diffuse cutaneous systemic sclerosis. J Rheumatol. 2010;37:116–24.
43. Daoussis D, Liossis SN, Tsamandas AC, Kalogeropoulou C, Paliogianni F, Sirinian C, Yiannopoulos G, Andonopoulos AP. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clin Exp Rheumatol. 2012;30:S17–22.
44. Elhai M, Meunier M, Matucci-Cerinic M, Maurer B, Riemekasten G, Leturcq T, Pellerito R, Von Mühlen CA, Vacca A, Airo P, Bartoli F, Fiori G, Bokarewa M, Riccieri V, Becker M, Avouac J, Müller-Ladner U, Distler O, Allanore Y, EUSTAR (EULAR Scleroderma Trials and Research group). Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study. Ann Rheum Dis. 2013;72:1217–20.
45. Pope J, McBain D, Petrich L, Watson S, Vanderhoek L, de Leon F, Seney S, Summers K. Imatinib in active diffuse cutaneous systemic sclerosis: results from a six-month, randomized, placebo-controlled, proof-of-concept study at a single center. Arthritis Rheum. 2011;63:3547–51.
46. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, Schuerwegh AJ, Marijt EW, Vonk MC, Schattenberg AV, Matucci-Cerinic M, Voskuyl AE, van de Loosdrecht AA, Daikeler T, Kötter I, Schmalzing M, Martin T, Lioure B, Weiner SM, Kreuter A, Deligny C, Durand JM, Emery P, Machold KP, Sarrot-Reynauld F, Warnatz K, Adoue DF, Constans J, Tony HP, Del Papa N, Fassas A, Himsel A, Launay D, Lo Monaco A, Philippe P, Quéré I, Rich É, Westhovens R, Griffiths B, Saccardi R, van den Hoogen FH, Fibbe WE, Socié G, Gratwohl A, Tyndall A, EBMT/EULAR Scleroderma Study Group. Autologous stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis. A randomized clinical trial. JAMA. 2014;311:2490–8.
47. De Rosa G, Pardeo M, Rigante D. Current recommendations for the pharmacologic therapy in Kawasaki syndrome and management of its cardiovascular complications. Eur Rev Med Pharmacol Sci. 2007;11:301–8.
48. Kaveri SV. Intravenous immunoglobulin: exploiting the potential of natural antibodies. Autoimmun Rev. 2012;11:792–4.
49. Seite JF, Shoenfeld Y, Youinou P, Hillion S. What is the contents of the magic draft IVIg? Autoimmun Rev. 2008;7:435–9.
50. Quinti I, Pesce AM, Bonanni L, Rubino C, Pulvirenti F, Milito C. Clinical use of polyvalent immunoglobulins. Blood Transfus. 2013;11:s33–9.
51. Debré M, Bonnet MC, Fridman WH, Carosella E, Philippe N, Reinert P. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. Lancet. 1993;342:945–9.
52. Kaneko Y, Nimmerjahn F, Madaio MP, Ravetch JV. Pathology and protection in nephrotoxic nephritis is determined by selective engagement of specific Fc receptors. J Exp Med. 2006;203:789–97.
53. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol. 2013;13:176–89.
54. Othy S, Hegde P, Topcu S, Sharma M, Maddur MS, Lacroix-Desmazes S, Bayry J, Kaveri SV. Intravenous gammaglobulin inhibits encephalitogenic potential of pathogenic T cells and interferes with their trafficking to the central nervous system, implicating sphingosine-1 phosphate receptor 1-mammalian target of rapamycin axis. J Immunol. 2013;190:4535–41.
55. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science. 2001;291:484–6.
56. Li N, Zhao M, Hilario-Vargas J, Prisayanh P, Warren S, Diaz LA, Roopenian DC, Liu Z. Complete FcRn dependence for intravenous Ig therapy in autoimmune skin blistering diseases. J Clin Invest. 2005;115:3440–50.
57. Anthony RM, Wermeling F, Karlsson MC, Ravetch JV. Identification of a receptor required for the anti-inflammatory activity of IVIG. Proc Natl Acad Sci USA. 2008;105:19571–8.
58. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science. 2006;313:670–3.
59. Parekh RB, Dwek RA, Sutton BJ, Fernandes DL, Leung A, Stanworth D, Rademacher TW, Mizuochi T, Taniguchi T, Matsuta K, et al. Association of rheumatoid arthritis and primary osteoarthritis with changes in the glycosylation pattern of total serum IgG. Nature. 1985;316:452–7.

60. Dube R, Rook GA, Steele J, Brealey R, Dwek R, Rademacher T, Lennard-Jones J. Agalactosyl IgG in inflammatory bowel disease: correlation with C-reactive protein. Gut. 1990;31:431–4.
61. Ephrem A, Chamat S, Miquel C, Fisson S, Mouthon L, Caligiuri G, Delignat S, Elluru S, Bayry J, Lacroix-Desmazes S, Cohen JL, Salomon BL, Kazatchkine MD, Kaveri SV, Misra N. Expansion of CD4+CD25+ regulatory T cells by intravenous immunoglobulin: a critical factor in controlling experimental autoimmune encephalomyelitis. Blood. 2008;111:715–22.
62. Barreto M, Ferreira RC, Lourenço L, Moraes-Fontes MF, Santos E, Alves M, Carvalho C, Martins B, Andreia R, Viana JF, Vasconcelos C, Mota-Vieira L, Ferreira C, Demengeot J, Vicente AM. Low frequency of CD4+CD25+ Treg in SLE patients: a heritable trait associated with CTLA4 and TGF-beta gene variants. BMC Immunol. 2009;10:5.
63. Sundblad A, Huetz F, Portnoï D, Coutinho A. Stimulation of B and T cells by in vivo high dose immunoglobulin administration in normal mice. J Autoimmun. 1991;4:325–39.
64. Paquin Proulx D, Aubin E, Lemieux R, Bazin R. Inhibition of B cell-mediated antigen presentation by intravenous immunoglobulins (IVIg). Clin Immunol. 2010;135:422–9.
65. Bayry J, Lacroix-Desmazes S, Carbonneil C, Misra N, Donkova V, Pashov A, Chevailler A, Mouthon L, Weill B, Bruneval P, Kazatchkine MD, Kaveri SV. Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. Blood. 2003;101:758–65.
66. Abe J, Jibiki T, Noma S, Nakajima T, Saito H, Terai M. Gene expression profiling of the effect of high-dose intravenous Ig in patients with Kawasaki disease. J Immunol. 2005;174:5837–45.
67. Ramakrishna C, Newo AN, Shen YW, Cantin E. Passively administered pooled human immunoglobulins exert IL-10 dependent anti-inflammatory effects that protect against fatal HSV encephalitis. PLoS Pathog. 2011;7:e1002071.
68. Ephrem A, Misra N, Hassan G, Dasgupta S, Delignat S, Duong Van Huyen JP, Chamat S, Prost F, Lacroix-Desmazes S, Kavery SV, Kazatchkine MD. Immunomodulation of autoimmune and inflammatory diseases with intravenous immunoglobulin. Clin Exp Med. 2005;5:135–40.
69. Bruhns P, Samuelsson A, Pollard JW, Ravetch JV. Colony-stimulating factor-1-dependent macrophages are responsible for IVIG protection in antibody-induced autoimmune disease. Immunity. 2003;18:573–81.
70. Anthony RM, Nimmerjahn F, Ashline DJ, Reinhold VN, Paulson JC, Ravetch JV. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. Science. 2008;320:373–6.
71. Prabagar MG, Choi HJ, Park JY, Loh S, Kang YS. Intravenous immunoglobulin-mediated immunosuppression and the development of an IVIG substitute. Clin Exp Med. 2013, epub ahead of print.
72. Baxley A, Akhtari M. Hematologic toxicities associated with intravenous immunoglobulin therapy. Int Immunopharmacol. 2011;11:1663–7.
73. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev. 2003;17:241–51.
74. Dantal J. Intravenous immunoglobulins: in-depth review of excipients and acute kidney injury risk. Am J Nephrol. 2013;38:275–84.
75. Bodemer C, Teillac D, Le Bourgeois M, Wechsler B, de Prost Y. Efficacy of intravenous immunoglobulins in sclerodermatomyositis. Br J Dermatol. 1990;123:545–6.
76. Wollina U, Looks A, Schneider R, Maak B. Disabling morphoea of childhood-beneficial effect of intravenous immunoglobulin therapy. Clin Exp Dermatol. 1998;23:292–3.
77. Levy Y, Sherer Y, Langevitz P, Lorber M, Rotman P, Fabrizzi F, Shoenfeld Y. Skin score decrease in systemic sclerosis patients treated with intravenous immunoglobulin—a preliminary report. Clin Rheumatol. 2000;19:207–11.
78. Levy Y, Amital H, Langevitz P, Nacci F, Righi A, Conforti L, Generini S, Matucci Cerinic M, Shoenfeld Y. Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: an open-label study. Arthritis Rheum. 2004;50:1005–7.
79. Asano Y, Ihn H, Asashima N, Yazawa N, Mimura Y, Jinnin M, Yamane K, Tamaki K. A case of diffuse scleroderma successfully treated with high-dose intravenous immune globulin infusion. Rheumatology. 2005;44:824–6.
80. Nacci F, Righi A, Conforti ML, Miniati I, Fiori G, Martinovic D, Melchiorre D, Sapir T, Blank M, Shoenfeld Y, Pignone AM, Cerinic MM. Intravenous immunoglobulins improve the function and ameliorate joint involvement in systemic sclerosis: a pilot study. Ann Rheum Dis. 2007;66:977–9.
81. Ihn H, Mimura Y, Yazawa N, Jinnin M, Asano Y, Yamane K, Tamaki K. High-dose intravenous immunoglobulin infusion as treatment for diffuse scleroderma. Br J Dermatol. 2007;156:1058–60.
82. Schanz S, Ulmer A, Fierlbeck G. Response of dystrophic calcification to intravenous immunoglobulin. Arch Dermatol. 2008;144:585–7.
83. Szekanecz Z, Aleksza M, Antal-Szalmás P, Soltész P, Veres K, Szántó S, Szabó Z, Végvári A, Szamosi S, Lakos G, Sipka S, Szegedi G, Varga J, Szücs G. 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.
84. Zandman-Goddard G, Krauthammer A, Levy Y, Langevitz P, Shoenfeld Y. Long-term therapy with intravenous immunoglobulin is beneficial in patients with autoimmune diseases. Clin Rev Allergy Immunol. 2012;42:247–55.
85. Takehara K, Ihn H, Sato S. A randomized, double-blind, placebo-controlled trial: intravenous immunoglobulin treatment in patients with diffuse cutaneous systemic sclerosis. Clin Exp Rheumatol. 2013;31:151–6.
86. Mauhin W, Rivière S, Cabane J, Tiev KP. Improvement in lung fibrosis using intravenous immunoglobulin in systemic sclerosis with myositis. Scand J Rheumatol. 2014;43:170–1.
87. Blank M, Levy Y, Amital H, Shoenfeld Y, Pines M, Genina O. The role of intravenous immunoglobulin therapy in mediating skin fibrosis in tight skin mice. Arthritis Rheum. 2002;46:1689–90.
88. Kajii M, Suzuki C, Kashihara J, Kobayashi F, Kubo Y, Miyamoto H, Yuuki T, Yamamoto T, Nakae T. Prevention of excessive collagen accumulation by human intravenous immunoglobulin treatment in a murine model of bleomycin-induced scleroderma. Clin Exp Immunol. 2011;163:235–41.
89. Kudo H, Jinnin M, Yamane K, Makino T, Kajihara I, Makino K, Honda N, Nakayama W, Fukushima S, Ihn H. Intravenous immunoglobulin treatment recovers the down-regulated levels of Th1 cytokines in the sera and skin of scleroderma patients. J Dermatol Sci. 2013;69:77–80.
90. Matsushita T, Hasegawa M, Hamaguchi Y, Takehara K, Sato S. Longitudinal analysis of serum cytokine concentrations in systemic sclerosis: association of interleukin 12 elevation with spontaneous regression of skin sclerosis. J Rheumatol. 2006;33:275–84.
91. Grassegger A, Schuler G, Hessenberger G, Walder-Hantich B, Jabkowski J, MacHeiner W, Salmhofer W, Zahel B, Pinter G, Herold M, Klein G, Fritsch PO. Interferon-g in the treatment of systemic sclerosis: a randomized controlled multicentre trial. Br J Dermatol. 1998;139:639–48.
92. Amemiya K, Semino-Mora C, Granger RP, Dalakas MC. Downregulation of TGF-beta1 mRNA and protein in the muscles of patients with inflammatory myopathies after treatment with high-dose intravenous immunoglobulin. Clin Immunol. 2000;94:99–104.

93. Molina V, Blank M, Shoenfeld Y. Intravenous immunoglobulin and fibrosis. Clin Rev Allergy Immunol. 2005;29:321–6.
94. Baleva M, Nikolov K. The role of intravenous immunoglobulin preparations in the treatment of systemic sclerosis. Int J Rheumatol. 2011;2011:829751.
95. Lidar M, Langevitz P. Pregnancy issues in scleroderma. Autoimmun Rev. 2012;11:A515–9.
96. Østensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, Doria A, Rai R, Meroni P, Cetin I, Derksen R, Branch W, Motta M, Gordon C, Ruiz-Irastorza G, Spinillo A, Friedman D, Cimaz R, Czeizel A, Piette JC, Cervera R, Levy RA, Clementi M, De Carolis S, Petri M, Shoenfeld Y, Faden D, Valesini G, Tincani A. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther. 2006;8:209.
97. Miniati I, Guiducci S, Mecacci F, Mello G, Matucci-Cerinic M. Pregnancy in systemic sclerosis. Rheumatology. 2008;47:16–28.