Clinical Immunology 199 (2019) 25–28

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Intravenous immunoglobulin (IVIG) in the vanguard therapy of Systemic Sclerosis

João Pedro Gomes[b,c,d,**], Lèlita Santos[c,d,**], Yehuda Shoenfeld[a,b,*]

[a] Sackler Faculty of Medicine, Tel Aviv University, Israel
[b] Zabludowicz Center for Autoimmune Disease, Sheba Medical Center, Tel Hashomer, Israel
[c] Department A of Internal Medicine, Hospital and University Centre of Coimbra, Coimbra, Portugal
[d] Faculty of Medicine, University of Coimbra, Portugal

ARTICLE INFO

Keywords:
Intravenous immunoglobulins (IVIG)
Systemic sclerosis
Autoimmunity
Autoimmune diseases
Fibrosis

ABSTRACT

Systemic Sclerosis (SSc) is a rare autoimmune disease that is characterized by a progressive skin fibrosis, an obliteration of the microvasculature and an exaggerated extracellular matrix deposition, which lead to a multisystemic dysfunction. Various pathogenetic mechanisms were described. The lack of a successful therapy make SSc a disease with a poor prognosis. The intravenous immunoglobulin (IVIG) has been used for a long time in different autoimmune diseases, and firstly used in SSc patients in 2000. IVIG has multiple non-specific mechanisms of action and, beyond an impressive improvement in muscle symptoms, a French nationwide cohort demonstrated that IVIG ameliorates the skin disease and systemic inflammation, and helps the daily dose corticosteroid's tapering at the end of the treatment. The benefits on gastrointestinal symptoms of IVIG was reported by a recent English article, in which the patients consistently reported a decrease in the gastro-esophageal reflux disease symptoms and their frequencies. The impact on the lung involvement still remains unclear. One of the advantages of IVIG is its safe profile. Few adverse effects were reported and most of them are mild, and can be managed and usually they do not relapse. Harmful effects were described, but they can be avoid with cautious and judicious use of this therapy.

1. Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease that is characterized by a progressive skin fibrosis, an obliteration of the microvasculature and an exaggerated extracellular matrix deposition [1]. Those phatophysiolofgical alterations result in a multi systemic dysfunction and the symptoms depend on the affliction of each organ. People with a diagnosis of SSc have a risk of mortality three- to five-times greater than the general population and the involvement of major organs (cardiac, interstitial lung disease, pulmonary hypertension and scleroderma renal crisis) affects the morbidity and increases the mortality [2].

SSc is classified into different clinical subsets, depending on skin involvement. The limited cutaneous SSc (lcSSc) is a subset characterized by skin sclerosis of the hands and feet distal to the elbows and knees, respectively, as well as the face [2]. This subset is usually associated with anticentromere and anti-Th/To antibodies [2]. On the other hand, the diffuse cutaneous SSc (dcSSc) is associated with the presence of anti-topoisomerase I and anti-RNA polymerase III antibodies, without a restricted skin involvement [2]. This last form has a high frequency of internal involvement and a rapidly progressive course of the disease, which affects the prognosis [2].

The therapy for SSc ranges between corticosteroids to hematopoietic stem cells transplantation, depending on the tissue affected [1]. Until today, none of the therapies have been described as a successful anti-fibrotic therapy [1] with a limited efficacy [3]. There are different reasons that can justified this unsuccessful response beyond SSc therapy: the underlying pathogenic mechanism of the disease is still

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; anti-RNA, anti-ribonucleic acid; dcSSc, diffuse cutaneous systemic sclerosis; IL, interleukin; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; lcSSc, limited cutaneous systemic sclerosis; mRSS, modified Rodnan skin score; SSc, systemic sclerosis; TGF, tumor growth factor

* Correspondence to: Y. Shoenfeld, Zabludowicz Center for Autoimmune Disease, Sheba Medical Center Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Tel Hashomer, Ramat Gan 52621, Israel.

** Corresponding authors at: Department A of Internal Medicine, Hospital and University Centre of Coimbra affiliated to Faculty of Medicine, University of Coimbra, Praceta Prof. Mota Pinto, 3000-075, Coimbra, Portugal.

E-mail addresses: jpcxl@hotmail.com (J.P. Gomes), lelitasantos@netcabo.pt (L. Santos), shoenfel@post.tau.ac.il (Y. Shoenfeld).

https://doi.org/10.1016/j.clim.2018.12.006

Available online 10 December 2018

Table 1
Protocol suggested for IVIG therapy in SSc.

Protocol for IVIG therapy in SSc	
Time when to start	Skin disease: early stage (mRSS ≤22 points) or refractory to corticosteroids, in dcSSc subset Arthritis: severe and refractory to anti-rheumatic medication Myositis: muscle weakness and muscle pain, refractory to corticosteroids Gastro-intestinal affliction: severe symptoms Lung disease: not enough studies
Protocol	Dose: 2 g per kg of IVIG Time: 3 to 4 days, lasting 7 to 8 h Frequency: Once a month Duration: 6 months
Gold standard targets	Skin disease: improvement of 5 points on mRSS, after the second treatment Arthritis: improvement of the symptoms and index of joint affliction (Ritchie index, Dreiser Algo-Functional Index, Pain visual analogue scale), after 6 months Muscle symptoms: improvement after 2 weeks of IVIG infusion Gastro-intestinal symptoms: improvement on the Gastro-Intestinal tract 2.0 questionnaire Lung: FVC (%) There's no study on the cost-effectiveness of IVIG in SSc

undefined; most of the interventional therapies are based on case series; in the cohort studies, the patients that were recruited were in different phases of the disease [3].

2. IVIG therapy and its biological role

Intravenous immunoglobulin (IVIG) has been used for a long time in various autoimmune diseases [4,5]. Its first use in SSc was described in 2000, in three patients that presented with a rapidly progressive manifestation of the disease, by Levy and colleagues [6]. IVIG is a human specific immunoglobulin G, that is derived from 6000 to 20,000 healthy blood donors. Beyond its multiple non-specific mechanisms of action, it has been used in different autoimmune diseases as hematologic diseases (idiopathic thrombocytopenic purpura), neurologic diseases (Guillain-Barré syndrome, acute myasthenia gravis and chronic idiopathic demyelinating polyneurophathy), dermatoses (pemphigus vulgaris, pemphigoid, toxic epidermal necrolysis and Steven-Johnson syndrome) or rheumatologic immune-related diseases (Kawasaki syndrome [7], dermatomyositis and ANCA-positive vasculitides) [1]. Recently, IVIG was used in refractory autoimmune disease with very interesting results [8–10], and even in a very rare autoimmune diseases like inflammatory myositis [11]. The rational use of IVIG includes its potent immunomodulatory action through neutralization of autoantibodies [12], inhibition of inflammatory mediators and blockage of Fc receptors on the surface of B cells [3]. The decrease of inflammatory mediators is well described in the studies of Blank et al. [13]. In this study, the decreasing levels in IL-4 and TGF-ß1 by splenocytes were observed in parallel with the decrease in collagen deposition and type I collagen expression in tight skin mice [13]. That data was confirmed in patients in a double-blind, placebo-controlled randomized clinical trial by a decrease Th1 cytokines in the sera and skin in patients with SSc [14].

No definite guidelines are available regarding the IVIG therapy [1,15], because case reports and cohort studies in which it has been used as a therapy in SSc, had reported different IVIG doses and various timing schemes options [6,14,15]. Beyond sera and tissue studies, the use of IVIG has shown to be clinically relevant; Levy and colleagues [16] demonstrated an improvement in the modified Rodnan skin score (mRSS) with a mean of 10 points (± 5,9; $p < 0{,}001$), in a two-center open label study, in which it was used at a 2 g/kg for 5 days monthly, for a period of 6 months. In 2015, Carrie L [17] corroborated this skin findings in a retrospective study of IVIG in refractory ative dcSSc, in which a sustain improvement of mRSS came along with an improvement of the skin responsiveness to mycophenolate mofetil. In Sanges' cohort study, the efficacy of IVIG in muscle-skeletal symptoms were shown too [18]. Sanges et al. [18] presented an improvement in muscle pain (74% vs 20%; $p < 0{,}0001$), muscle weakness (45% vs 21%; $p = 0{,}01$), joint pain (44% vs 19%; $p = 0{,}02$) and serum creatine-kinase levels (1069 ± 1552UI vs 288 ± 449UI; $p < 0{,}0001$) after at least 1 g/kg/cycle of IVIG [18]. Muscle improvement could be expected within two weeks after the first infusion of IVIG, yet [19]. In a Portuguese case report, the improvement was reported as early as after one week of treatment [15]. The efficacy of IVIG on the gastrointestinal tract was recently demonstrated by Raja et al. [20]. He published an improvement in gastro-esophageal reflux disease symptoms and frequency and an overall improvement in gastrointestinal tract symptoms [20], like we presented previous in ours case report. These findings confirm the trend showed by Sanges et al. [18] in a French nationwide cohort and its mechanism is based upon the effect of IVIG to muscarinic-3 receptor antibody activity on gastrointestinal tract [21]. Kumar et al. [21] has demonstrated that IVIG reverses the cholinergic dysfunction at the myogenic and neural receptors by anti-idiotypic neutralization of SScIgG, which supports the clinical findings. One of the interesting findings of the IVIG therapy is the effect on decreasing corticosteroids daily dose. Sanges et al. [18] in their study, demonstrated a significantly lower corticosteroid need at the end of the treatment with IVIG (13,0 ± 11,6 mg/day vs 8,9 ± 10,4 mg/day; $p = 0{,}01$), results which have been replicated in others case reports [15]. Sanges et al. findings have also demonstrated that IVIG has a benefit on the systemic inflammation by a decreasing levels of C-reactive protein (13,1 ± 17,6 mg/L vs 9,2 ± 16,6 mg/L; $p = 0{,}001$) [18]. One of the most challenging and harmful clinical aspects on SSc is the lung disease. The different strategies that have been used to slow down the progression of interstitial lung disease (ILD) related to SSc have shown only a mild impact [12–26]. A case report of a 53-years old woman with SSc with myositis, recently diagnosed with ILD and treated with IVIG 2 g/kg monthly had clinical and radiologic improvement after 6 months of IVIG therapy [21]. Although these improvement was not corroborated in more recent cohort study, this study was constituted by a heterogeneous group of patients, which can be a limitation on its results [18]. In Sanges' study [18], most of the radiologic changes were maintained stable, although they have not demonstrated a significantly difference. On the other hand, an exploratory multicenter, non-randomized and prospective trial of IVIG in 10 patients diagnosed with idiopathic pulmonary fibrosis has shown that IVIG could be effective in the improvement of the lung involvement [27]. In the Table 1, is suggested a protocol for IVIG therapy in SSc.

New generation molecules, like organized multiuser of IgG Fc-fragments and monoclonal antibodies to FcRn, are under development and may be able to mimic several mechanisms of IVIG, possibility of IVIG at lower doses. [28]

2.1. The safety profile of IVIG

One of the advantage of IVIG is its safety profile [29]. The reported incidence of adverse event varies between 1% to 81%, but most report this events in 30% to 40% of the infusions [30,31]. The immediate adverse reactions are usually mild and transient [32]. Those adverse reactions may develop during the first hour after the infusion and can last for up to 24 h, and, usually, occur in the first and second treatment session [32]. Their etiology remains uncertain and they improve or wane following reduction of the infusion flow [30]. Most of these reactions are flu-like symptoms and include headache (the most common), face flushing, malaise, chills, fever, vomiting, diarrhea, nausea, myalgia, back pain, fatigue, dyspnea, changes in blood pressure and tachycardia [30,31,33–35]. Pretreatment with analgesics, non-steroidal anti-inflammatory, anti-histamines or even intravenous glucocorticoids may prevent these immediate adverse reactions [36], but it is only required if patient has developed one or more adverse events previously [32]. The late adverse events may be severe and include acute renal failure, thrombotic events (the two most common), aseptic meningitis, neutropenia, autoimmune hemolytic anemia, skin reactions, arthritis and pseudohyponatremia [29]. The acute renal failure has been related to the incipient (sucrose, a stabilizer) and usually occurs in the first ten days after IVIG infusion. This event is usually oliguric and reversible, but up to 40% of the cases emergency hemodialysis is required. Pre-existing renal condition, poor hydration, elderly age (> 65 years old), diabetes, hypertension, hyperviscosity and concomitant treatment with other nephrotoxic agent are risk factors to acute renal failure. Though, good hydration, slow infusion rates, a monitoring urine output and kidney function, and avoidance of sucrose preparations are recommended to prevent this complication of IVIG [37]. Thrombotic events (myocardial infractions, cerebrovascular accidents, deep vein thrombosis and pulmonary emboli) have been described during or following IVIG administration and its occurrence has been associated with advance age, atherosclerosis, previous thromboembolic events, excessive doses or fast IVIG infusions and the content of factor XIa [38]. To prevent the thrombotic complications, it is recommended to avoid this therapy on patients with multiple risk factors and it should be delivered in a slow infusion: 2 g/kg of body weight over 5 days, 0,4 g/kg/day in not < 8 h [38]. Most of the IVIG today went through a new process to remove several coagulation factors (II, VII, IX, X, and particularly XIa) [39]. This process results in a procoagulant activity below the detection limit (except by non-activated partial thromboplastin time), suggesting a reduced risk of thromboembolic events with new IVIG products [39]. In a series of 56 patients treated with IVIG due to different autoimmune conditions, adverse events occurs in 36%, most of them were mild [31]. In only one patient a thrombotic event was related to this therapy was described — a superficial thrombosis related to the infusion vein [29]. In a recent retrospective study involving 46 patients diagnosed with SSc and treated with IVIG, 20% of mild events were reported (three patients had chills and fever; three had skin rash; three had headache) and only 4% of severe events (one patient had deep vein thrombosis and another had a diffuse edematous syndrome), which demonstrate the safety of IVIG in SSc [18]. Another aspect of the safety of IVIG therapy is that it is not associated with an increased risk of infection, which distingues it from the others therapeutics of the disease [18].

3. Conclusion

SSc is a rare currently disease, that have two different subsets differentiated by skin affliction. SSc lacks a successful therapy. The rational use of IVIG in SSc has a pathological background and recent studies show IVIG as an efficacious and safe therapy in SSc. Its success is so far described on muscle, skin and joint involvement as well in corticosteroid tapering. The lung disease is still a challenge, but more studies are required. If the patients are judicious recruited (early stages), and the infusion is made in a slow rate and with a good hydration, IVIG seems safe.

References

[1] L. Cantarini, D. Rigante, A. Vitale, S. Napodano, L.I. Sakkas, D.P. Bogdanos, Y. Shoenfeld, Intravenous immunoglobulins (IVIG) in systemic sclerosis: a challenge yet promising, Immunol. Res. 61 (3) (2015 Mar) 326–337.

[2] K. Yanab, Strategy of treatment of fibrosis in systemic sclerosis: present and future, J. Dermatol. 43 (1) (2016 Jan) 46–55.

[3] T.M. Frech, V.K. Shanmugam, A.A. Shah, S. Assassi, J.K. Gordon, F.N. Hant, M.E. Hinchcliff, V. Steen, D. Khanna, C. Kayser, R.T. Domsic, Treatment of diffuse systemic sclerosis skin disease, Clin. Exp. Rheumatol. 31 (2 Suppl 76) (2013 Mar-Apr) 166–171.

[4] E. Hachulla, A. Wibaux, P.Y. Hatron, U. Michon-Pasturel, V. Queyrel, A.L. Fauchais, B. Devulder, M.N. Lefebvre, M. Yilmaz, House sequential high dose intravenous immunoglobulins in systemic autoimmune diseases, Ann. Rheum. Dis. 61 (3) (2002 Mar) 277–278.

[5] S. Kivity, U. Katz, N. Daniel, U. Nussinovitch, N. Papageorgiou, Y. Shoenfeld, Evidence for the use of intravenous immunoglobulins — a review of literature, Clin. Rev. Allergy Immunol. 38 (2–3) (2010 Apr) 201–269.

[6] Y. Levy, Y. Sherer, P. Langevitz, M. Lorber, P. Rotman, F. Fabrizzi, Y. Shoenfeld, Skin score decrease in systemic sclerosis patients treated with intravenous immunoglobulin - a preliminary report, Clin. Rheumatol. 19 (3) (2000) 207–211.

[7] J.B. Fraison, P. Sève, C. Dauphin, A. Mahr, E. Gomard-Mennesson, L. Varron, G. Pugnet, C. Landron, P. Roblot, E. Oziol, G. Chalhoub, J.M. Galempoix, S. Humbert, P. Humbert, E. Sbidian, F. Grange, O. Bayrou, P. Cathebras, P. Morlat, O. Epaulard, P. Pavese, du L.T. Huong, A. Zoulim, K. Stankovic, H. Bachelez, A. Smail, C. Bachmeyer, B. Granel, J. Serratrice, G. Brinchault, A. Mekinian, N. Costedoat-Chalumeau, A. Bourgarit-Durand, X. Puéchal, L. Guillevin, M. Piram, I. Koné-Paut, O. Fain, CRI and the French Vasculitis Study Group. Kawasaki disease in adults: Observations in France and literature review, Autoimmun. Rev. 15 (3) (2016 Mar) 242–249.

[8] S. Tenti, M. Fabbroni, V. Mancini, F. Russo, M. Galeazzi, A. Fioravanti, Intravenous immunoglobulins as a new opportunity to treat discoid lupus erythematosus: a case report and review of the literature, Autoimmun. Rev. 17 (8) (2018 Jun 6).

[9] S. Tenti, S. Cheleschi, G.M. Guidelli, M. Galeazzi, A. Fioravanti, Intravenous immunoglobulins and antiphospholipid syndrome: how, when and why? A review of the literature, Autoimmun. Rev. 15 (3) (2016 Mar) 226–235.

[10] L. Cantarini, M.L. Stromillo, A. Vitale, G. Lopalco, G. Emmi, E. Silvestri, A. Federico, M. Galeazzi, F. Iannone, N. De Stefano, Efficacy and safety of intravenous immunoglobulin treatment in refractory Behcet's disease with different organ involvement: a case series, Isr. Med. Assoc. J. 18 (3–4) (2016 Mar-Apr) 238–242.

[11] P. Cherin, C. Belizna, O. Cartry, G. Lascu-Dubos, C. de Jaeger, J.C. Delain, J.C. Crave, E. Hachulla, Long-term subcutaneous immunoglobulin use in inflammatory myopathies: a retrospective review of 19 cases, Autoimmun. Rev. 15 (3) (2016 Mar) 281–286.

[12] M. Blank, T. Bashi, Y. Shoenfeld, Idiotype-specific intravenous immunoglobulin (IVIG) for therapy of autoimmune diseases, Chapter 18, in: Michael Steinitz (Ed.), Human Monoclonal Antibodies: Methods and Protocols, Methods Mol. Biol. 1060 2014, pp. 353–361.

[13] M. Blank, Y. Levy, H. Amital, Y. Shoenfeld, M. Pines, O. Genina, The role of intravenous immunoglobulin therapy in mediating skin fibrosis in high skin mice, Arthritis Rheum. 46 (6) (2002 Jun) 1689–1690.

[14] H. Kudo, M. Jinnin, K. Yamane, T. Makino, I. Kajihara, K. Makino, N. Honda, W. Nakayama, S. Fukushima, H. Ihn, Intravenous immunoglobulin treatment recovers the down-regulated levels of Th1 cytokines in the sera and skin of scleroderma patients, J. Dermatol. Sci. 69 (1) (2013 Jan) 77–80.

[15] J. Abelha-Aleixo, A. Bernardo, L. Costa, Benefit of intravenous immunoglobulin in a patient with longstanding polymyositis/systemic sclerosis overlap syndrome, Acta Reumatol. Port. 40 (2) (2015 Apr-Jun) 176–178.

[16] Y. Levy, H. Amital, P. Langevitz, F. Nacci, A. Righi, L. Conforti, S. Generini, M. Matucci Cerinic, Y. Shoenfeld, Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: an open-label study, Arthritis Rheum. 50 (3) (2004 Mar) 1005–1007.

[17] C.L. Poelman, L.K. Hummers, F.M. Wigley, C. Anderson, F. Boin, A.A. Shah, IVIG may be an effective therapy for refractory, active diffuse cutaneous scleroderma, J. Rheumatol. 42 (2) (2015 Feb) 236–242.

[18] S. Sanges, S. Rivière, A. Mekinian, T. Martin, A. Le Quellec, E. Chatelus, A. Lescoat, P. Jego, C. Cazalets, T. Quéméneur, N. Le Gouellec, P. Senet, C. Francès, A. Deroux, B. Imbert, O. Fain, L. Boukari, T. Sené, C. Deligny, A. Mathian, C. Agard, G. Pugnet, S. Speca, S. Dubucquoi, P.Y. Hatron, É. Hachulla, D. Launay, Intravenous immunoglobulins in systemic sclerosis: data from a French nationwide cohort of 46 patients and review of the literature, Autoimmun. Rev. 16 (4) (2017 Apr) 377–384.

[19] R. Aggarwal, C.V. Oddis, Therapeutic approaches in myositis, Curr. Rheumatol. Rep. 13 (3) (2011 Jun) 182–191.

[20] J. Raja, S.I. Nihtyanova, C.D. Murray, C.P. Denton, V.H. Ong, Sustained benefit from intravenous immunoglobulin therapy for gastrointestinal involvement in systemic sclerosis, Rheumatology (Oxford) 55 (1) (2016 Jan) 115–119.

[21] S. Kumar, J. Singh, R. Kedika, F. Mendoza, S.A. Jimenez, E.S. Blomain, A.J. Dimarino, S. Cohen, S. Rattan, Role of muscarinic-3 receptor antibody in systemic sclerosis: correlation with disease duration and effects of IVIG, Am. J. Physiol. Gastrointest. Liver Physiol. 310 (11) (2016 Jun 1) G1052–G1060.

[22] D.P. Tashkin, R. Elashoff, P.J. Clements, J. Goldin, M.D. Roth, D.E. Furst, E. Arriola,

R. Silver, C. Strange, M. Bolster, J.R. Seibold, D.J. Riley, V.M. Hsu, J. Varga, D.E. Schraufnagel, A. Theodore, R. Simms, R. Wise, F. Wigley, B. White, V. Steen, C. Read, M. Mayes, E. Parsley, K. Mubarak, M.K. Connolly, J. Golden, M. Olman, B. Fessler, N. Rothfield, M. Metersky, Scleroderma Lung Study Research Group, Cyclophosphamide versus placebo in scleroderma lung disease, N. Engl. J. Med. 354 (25) (2006 Jun 22) 2655–2666.

[23] R.K. Hoyles, R.W. Ellis, J. Wellsbury, B. Lees, P. Newlands, N.S. Goh, C. Roberts, S. Desai, A.L. Herrick, N.J. McHugh, N.M. Foley, S.B. Pearson, P. Emery, D.J. Veale, C.P. Denton, A.U. Wells, C.M. Black, du Bois RM. a multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma, Arthritis Rheum. 54 (12) (2006 Dec) 3962–3970.

[24] S.C. Plastiras, P.G. Vlachoyiannopoulos, G.E. Tzelepis, Mycophenolate mofetil for interstitial lung disease in scleroderma, Rheumatology (Oxford) 45 (12) (2006 Dec) 1572.

[25] R.F. Spiera, J.K. Gordon, J.N. Mersten, C.M. Magro, M. Mehta, H.F. Wildman, S. Kloiber, K.A. Kirou, S. Lyman, M.K. Crow, Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of 1-year, phase IIa, single-arm, open-label clinical trial, Ann. Rheum. Dis. 70 (6) (2011 Jun) 1003–1009.

[26] W. Mauhin, S. Rivière, J. Cabane, K.P. Tiev, Improvement in lung fibrosis using intravenous immunoglobulin in systemic sclerosis with myositis, Scand. J. Rheumatol. 43 (2) (2014) 170–171.

[27] N. Enomoto, K. Chida, T. Suda, Y. Kaida, M. Taniguchi, A. Azuma, H. Hayashi, T. Ogura, H. Kitamura, O. Yamaguchi, M. Ando, A. Sato, S. Kudo, An exploratory trial of intravenous immunoglobulin therapy for idiopathic pulmonary fibrosis: a preliminar multi center report, Clin. Respir. J. 10 (6) (2016 Nov) 746–755.

[28] A.W. Zuercher, R. Spirig, A. Baz Morelli, F. Käsermann, IVIG in autoimmune disease - Potential next generation biologics, Autoimmun. Rev. 15 (8) (2016 Aug) 781–785.

[29] U. Katz, A. Achiron, Y. Sherer, Y. Shoenfeld, Safety of intravenous immunoglobulin (IVIG) therapy, Autoimmun. Rev. 6 (4) (2007 Mar) 257–259.

[30] H. Orbach, U. Katz, Y. Sherer, Y. Shoenfeld, Intravenous immunoglobulin: adverse effects and safe administration, Clin. Rev. Allergy Immunol. 29 (3) (2005 Dec) 173–184.

[31] Y. Sherer, Y. Levy, P. Langevitz, L. Rauova, F. Fabrizzi, Y. Shoenfeld, Adverse effects of intravenous immunoglobulin therapy in 56 patients with autoimmune diseases, Pharmacology 62 (3) (2001) 133–137.

[32] P. Cherin, I. Marie, M. Michallet, E. Pelus, J. Dantal, J.C. Crave, J.C. Delain, J.F. Viallard, Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence, Autoimmun. Rev. 15 (1) (2016 Jan) 71–81.

[33] Y. Shoenfeld, U. Katz, IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients, Autoimmunity 38 (2) (2005 Mar) 123–137.

[34] J.R. Pierce, N. Jain, Risks associated with the use of intravenous immunoglobulin, Transfus. Med. Rev. 17 (4) (2003 Oct) 241–251.

[35] M. Wittstock, R. Benecke, U.K. Zettl, Therapy with intravenous immunoglobulins: complications and side-effects, Eur. Neurol. 50 (3) (2003) 172–175.

[36] A. Ruetter, T.A. Luger, Efficacy and safety of intravenous immunoglobulin for immune-mediated skin disease: current view, Am. J. Clin. Dermatol. 5 (3) (2004) 153–160.

[37] H. Orbach, M. Tishler, Y. Shoenfeld, Intravenous immunoglobulin and kidney - a two-edged sword, Semin Arthritis Rheum. 34 (3) (2004 Dec) 593–601.

[38] U. Katz, Y. Shoenfeld, Review: intravenous immunoglobulin therapy and thromboembolic complications, Lupus 14 (10) (2005) 802–808.

[39] D.H. Park, G.B. Kang, D.E. Kang, J.W. Hong, M.G. Lee, K.Y. Kim, Han JW. A new manufacturing process to remove thrombogenic factors (II, VII, IX, X, and XI) from intravenous immunoglobulin gamma preparations, Biologicals 45 (2017 Jan) 1–8.