Systemic lupus erythematosus and its treatment with intravenous immunoglobulins (IVIG).

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by a broad array of clinical signs. In this study, we aimed to use intravenous immunoglobulins (IVIG), called intacglobin, as a monotherapy to manage SLE in three patients. Laboratory investigations for SLE diagnosis were performed, including the detection of anti-nuclear antibodies (ANA) and SLE confirmation by detecting high titers of anti-dsDNA antibodies. C3 and C4 serum levels were assessed, as well as the determination of immunoglobulins. The SLEDAI score was measured to determine whether a significant degree of disease activity existed and as a prognostic value. The evaluation of any chest infection was performed by chest-X-ray. The patients were treated with five–ten g/day of IVIG for six consecutive days, followed by five–ten g/month. Immunological evaluation demonstrated that patients presented with a flare of SLE with high titers of ANA and anti-dsDNA antibodies, low C3 and C4, and elevated immunoglobulin levels. The SLEDAI score falls from 10 to below 3, and chest infections in some patients are cleared up. The postulated mechanisms of action of IVIG demonstrated that it could be used as an immunosuppressor, immunomodulator, and antimicrobial agent in patients with SLE.

Keywords: Systemic lupus erythematosus (SLE), Intravenous immunoglobulins (IVIG), Autoantibody, Autoimmune disease, Pneumonia.

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder. It develops in genetically prone patients, where the influence of various environmental factors causes the development of many autoantibodies. It is a common autoimmune disease. A wide array of clinical manifestations characterizes this condition. The most common signs of illness are photosensitivity, oral ulcers, pleuritis, pneumonia, pericarditis, arthritis, kidney problems, blood cell abnormalities, seizures, and psychosis. Antibodies in SLE react with the critical components of the cell nucleus [1-3].

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SLE is mainly a condition in young women, which may occur from infancy to old age. It peaks between the ages of 15-40. Females are mostly affected (6-10:1), and blacks (and possibly Hispanics, Asians, and Native Americans) are affected more than whites [2,3].

The SLE prevalence of SLE varies worldwide and ranges as high as 1,500,000 cases, as reported by the Lupus Foundation of America [4]. A recent study estimated a 2005 incidence of 161,000 with definite SLE and 322,000 with definite or probable SLE [5].

IVIG is a product prepared from fractioning pools of thousands of plasma donations and is collected from blood transfusion services [6-9]. Other proteins, such as traces of IgM and IgA, cytokines, and immunomodulating peptides [10], can be prepared along with purified IgG. This paper describes a compelling case of a young woman with pneumonia and systemic manifestations of SLE who was treated with IVIG produced at "*Serum and Blood*-Derivative *Products Company* "*Adalberto Pesant*" Adalberto Pesant, called intacglobin.

Material and **Methods**

This was a descriptive, prospective study in which three patients with systemic lupus erythematosus were followed up for 36 months. After consent form were signed they were treated with Intacglobin, an intravenous immunoglobulin for national production in Cuba. Several laboratory studies were performed, but we stressed on those immunological studies that help to evaluate the response of patients to treatment, including quantification of immunoglobulins, the presence of antinuclear antibodies, double stranded DNA antibody, C3and C4, 24h urine protein measurement, and complete blood count among other markers. Using the revised criteria of the American College of Rheumatology (ACR), diagnosis of lupus was confirmed, and disease activity was confirmed using the SLE Disease Activity Index (SLEDAI) 2000 score. A score ≥3 was considered an active disease. A score of 3 was considered inactive.

Results

Case presentation one.

This is the case for a woman with well-known SLE that has been previously reported [11,12]. A 23-year-old white woman was sent to the Freyre de Andrade Hospital, Havana City, Cuba, with symptoms of malaise. She was well until a week ago, when she developed polyarthralgia, skin manifestations, and complaints of a chest infection, including productive cough with yellow mucus, shortness of breath, and stabbing chest pain [12]. Since the age of 16 years, she was diagnosed with SLE and since that age, she has been admitted various times for evaluation and treatment.

Vital signs recorded the presence of fever (101°F), oxygen saturation of 97% at room air, heart rate of 105 beats/min, and respiratory rate of 22 breaths/min. Pulmonary examination revealed the presence of crackles, wheezing, and decreased breath sounds. A complete blood cell count showed the presence of leukopenia (2600/mm3). Hemoglobin level of 9.8 g/dL and erythrocyte sedimentation rate of 68 mm/h.

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Antinuclear antibodies (ANA) were present at a titer of 1/2000 with a homogeneous pattern. Laboratory findings included proteinuria, increased gammaglobulin fraction on serum protein electrophoresis, and a C-reactive protein (CRP) level of 165 mg/L. In addition, anti-dsDNA antibodies were found at a concentration of 98 IU/mL, along with low levels of C3 and C4. The HIV, HBV, and HCV serologies were negative. Chest radiography revealed features of pleural effusion and lobal consolidation in the right lung, which was consistent with lobal pneumonia. In sputum and blood culture was isolated Streptococcus pneumoniae using standard microbiological techniques.

This woman was a well-known SLE case that explains why she was managed in the past with non-steroidal anti-inflammatory drugs, IVIG, corticosteroids, and immunosuppressants. Her physical examination showed that she had arterial hypertension (150/100 mmHg). She had a classic “butterfly rash” and other signs of vasculitis, in addition to signs of pericardial friction rub, and echocardiography confirmed a moderate-sized pericardial effusion.

The patient was sent to the intensive care unit (ICU), where she was treated with 10 g/day of IVIG for six consecutive days. There was marked clinical improvement in pulmonary manifestations after the completion of immunotherapy with IVIG. Additionally, there was an improvement in skin and cardiovascular problems.

Laboratory findings showed an increase in the activity of the hemolytic complement, lower titers of anti-dsDNA, and anti-red blood cell antibodies. Chest radiography showed resolution of pleurisy and lobal pneumonia. The patient was transferred to the Internal Medicine ward, where she was followed up for five days, after which she was sent home.

She was also treated with IVIG (10 g per month). Clinically and humoral remission was achieved for a10 months, where she did not complain of other signs and symptoms of chest infection or other SLE manifestations. The SLEDAI score was assessed to evaluate the clinical status and showed a score of 12 and < 3 before and after IVIG treatment, respectively. The patient remained in remission with few altered serological parameters.

The experiment was conducted with the understanding and consent of the human subjects, and the Ethical Committee of the “Freyre de Andrade”’ Teaching Hospital, Havana, Cuba approved the experiments.

Case presentation two.

It is the case of another 34-year-old white male that presented with a history of asthenia, psychological depression, generalized skin rash, previous recurrent respiratory tract infections, angioneurotic edema, and arthritis. The patient was suspected of having SLE and was treated with prednisone, antibiotics, and non-steroid anti-inflammatory drugs without complete remission of the disease.

On admission, his laboratory findings were marked anemia (7.5 g/L), decreased C4 and C3, positive Coomb's test, increased circulating immunocomplexes, hypergammaglobulinemia, presence of anti-nuclear antibodies, and high titer of anti-dsDNA antibodies. Chest radiography

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revealed a discrete right pleural effusion. He was treated with five g/day IVIG for five consecutive days. After treatment, the most critical findings were the remission of vasculitis and polyarthritis. There was a vital remission of humoral findings, such as C3 and C4, after treatment completion. The patient was further treated with 10 g/month of IVIG, and no other SLE crisis was observed in one year of evaluation, except for an intermittent episode of upper respiratory tract infection without significant consequences. Before treatment, the SLEDAI score was 18, which was a severe flare; after treatment with IVIG, the score was less than 3. He has kept for 3 years on a monthly dose of IVIG of 10g/months.

Case presentation three.

A 49-year-old white man was admitted by reporting that he was exposed to sunlight daily at his workplace. He was placed on prednisone but was noncompliant. He also complained of asthenia, weight loss and anorexia. Physical examination revealed skin lesions, including a “butterfly rash,” and erythematous plaques and papules. In addition, extensive oropharyngeal ulcers, vasculitis, and alopecia were observed. Other positive clinical data included polyarthritis and hyperreflexia.

Immunological studies showed positive antinuclear antibodies, anti-dsDNA antibodies, low C3 levels, leucopenia, impaired cellular immunity, positive Coomb’s test, and false-positive Venereal Disease Research Laboratory (VDRL). A dosage of 5 g/day of IVIG was administered for five consecutive days; after the third dose of IVIG, a clinical improvement was observed. Abnormal laboratory findings were resolved. Indeed, the patient was followed up in the outpatient rheumatology and immunology clinic for a year, and he showed no clinical or humoral exacerbation of SLE as a normal SLEDAI score of < three. He has kept for 3 years on a monthly dose of IVIG of 5g/month. At week 20, we manifested a SLEDI score of 5, predominantly hematological manifestations, but the dose of Intacglobin was increased to 10g/month since then he had an inactive disease during the period of study period.

During the duration of this study, all patients were maintained without the use of NSAIDs, anti-malarial drugs, steroids and immunosuppressors.

Discussion

The use of purified IgG to treat both SLE crisis and pneumonia caused by pneumococci is described. The lung infection seen in SLE is mostly due to staphylococci and is treated with antibiotics. Here, we demonstrated that both SLE and bacterial pneumonia could be treated with IVIG only, without the need for steroids or immunosuppressors due to the immunosuppressive effects of IVIG and the presence of a wide range of anti-bacterial antibodies.

A dosage of 5-10 g/day of IVIG was used for six consecutive days during the SLE crisis, and then 10 g monthly was used as a maintenance dose. A reduction in the SLEDAI score proved the beneficial effects of purified IgG therapy in this case.

IVIG was useful for the clearance of pneumonia and other manifestations of lupus.

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This case required a higher immunoglobulin dose because she experienced an acute respiratory infection, in addition to vasculitis [8]. In addition, IVIG therapy was sufficient to control other subclinical infections associated with SLE, as antibodies directed against a broad spectrum of microorganisms, including bacteria, can be present at high levels in the IVIG [9].

SLE patients are immunodeficient because of the nature of the disease and immunotherapy used to suppress the immune system. Recurrent chest infections may be a late clinical manifestation of this autoimmune disease. Garcia-Guevara et al. (2018) reported that pneumonia remains the leading cause of mortality in patients with systemic lupus erythematosus (SLE), and the most common bacteria isolated are *S. aureus*, but other genera of bacteria have been cited [10-11].

In this study, *S. pneumoniae* was detected in blood cultures and presented as a cause of pneumonia and bacteremia. Pulmonary systemic lupus erythematosus (SLE) may manifest as lupus pneumonitis that can mimic acute infectious pneumonia in all clinical and radiographic). Both presented with fever, dyspnea, and chest pain. Infectious microorganisms have recently been isolated. IVIG has an antimicrobial effect against viruses and bacteria [8,12] through neutralization and opsonization. In addition, it has a positive effect on activated B cells that contribute to the production of specific antibodies against bacterial antigens, and exogenous intravenous immunoglobulins play a critical role in the immunotherapy of SLE [12-16].

The worldwide consumption of IVIG increased from 300 kg in 1980 to 100 tons per year in 2010 [17]. The mechanisms of action of IVIG reflect the influence of natural antibodies in maintaining immune homeostasis [18]. IVIG's side effects are mild and transient and can be minimized by administering a slow infusion rate of 0.4 g/Kg IVIG's body weight for five consecutive days and given in monthly cycles. The high price is the only IVIG downside treatment [19]. The transmission risk of microorganisms appears theoretically [20]. Intravenous immunoglobulins are not recommended for eight conditions, including autism, adrenoleukodystrophy, and critical illness polyneuropathy. Other conditions were:

- amyotrophic lateral sclerosis,
- intractable childhood epilepsy,
- paraproteinemic neuropathy (IgM variant),
- inclusion body myositis, and
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy or edema, M-protein, and skin abnormalities)

The development of evidence-based clinical practice guidelines may facilitate the appropriate use of the 21 guidelines. The immunomodulatory mechanisms of IVIG are not well understood because of the diversity and often contradictory mechanisms (Fc, F(ab')(2), and non-IgG-related). The results obtained in various *in vivo* and *in vitro* experimental models have been contradictory [3].

Immunoglobulin therapy started in 1930 when, in Finland, Cohn, Bruton, and Imbach carried out pneumococcal pneumonia treatment in patients with equine serum. It notably improved the survival rate of this type of pneumonia. IVIG was originally used to treat immunodeficiencies. IVIG was later extended to treat inflammatory and autoimmune disorders [19]. IVIG has been

successfully used to treat SLE with a large spectrum of clinical manifestations, such as refractory thrombocytopenia, pancytopenia, central nervous system (CNS) involvement, secondary antiphospholipid syndrome, and lupus nephritis [22].

IVIG's modes of action involve interference with activation of complement components and the cytokine network, effects on Tregs, expression of Fc receptors, and modulation of the idiotype network, among other mechanisms. The therapeutic effects of IVIG most likely reflect natural antibody functions, which play an essential role in maintaining immune homeostasis in healthy individuals.

Thus, the use of IVIG as a therapeutic agent for arthritis is significant. In the United States, the prevalence of this disorder is high and ethnicity plays a role. Helmick and colleagues published in 2008 that 21% of USA adults were found to have self-reported doctor-diagnosed arthritis. They estimated that systemic lupus erythematosus affects up to 322,000 adults, rheumatoid arthritis affects 1.3 million adults, spondyloarthropathy affects up to 2.4 million adults, juvenile arthritis affects 294,000 children, systemic sclerosis affects 49,000 adults, and primary Sjögren's syndrome affects up to 3.1 million adults [23]. All these conditions may benefit from IVIG treatment. In addition to many other problems, such as other autoimmune disorders, immunodeficiency [24,25], and inflammatory disorders could be treated with IVIG, which is considered an issue of concern in specialized medical fields worldwide.

Among IVIG's action mechanisms are effects on activated B lymphocytes [26]; potential involvement of IgG autoantibodies in the IVIG's immunomodulatory effects [27]; anti-idiotypic specificity presence that may not necessarily be detectable in blood from single healthy individuals [28,29]; identification of the same idiotypic determinants on autoantibodies by anti-idiotypic antibodies present in the IVIG [30]; holding of autoantibodies on IVIG's sepharose-affinity column bound F(ab')2 fragments supports that intravenous immunoglobulins interacts with autoantibodies in SLE and other autoimmune disorders [30]; IVIG infusion results in suppression of specific auto-IgG clones *in vivo* [31,32]; IVIG interacts with V regions of autoantibodies and with lymphocyte's surface molecules *in vitro* [33, 34]; interaction of the IgG Fc fragment from IVIG with Fc receptors on leukocytes and endothelial cells [35]; IVIG interacts with constant regions of the beta chain of the alpha-beta T cell receptor [31]; interaction of infused IgG with complement proteins [36].

IVIG causes lymphocyte and monocyte modulation of the release of cytokines and cytokine antagonists [37], promotes cell proliferation modulation and apoptosis [38] and neutralizes pathogenic autoantibodies [39]. IVIG causes functional Fc receptor blockade on splenic macrophages [40], interferes with antigen presentation [41], interacts with T cell surface molecules such as the alpha-beta TCR, CD4, CD5, and MHC class I molecules' non-polymorphic determinants of T and B cell adhesion molecules [31,40], and neutralizes bacterial toxins and superantigens [42-44]. Studies are on their way to clarify the use of some immunotherapy including interleukins in SLE treatment, which would not have the toxic effects of steroids and immunosuppressors as far as we know[45-46]. We conclude that Intacglobin was successfully used in the treatment of these series of cases with systemic lupus erythematosus and we recommend it as a substitute for the traditional therapy, which is toxic.

Conflict of interest: The authors declare that there are no conflicts of interest regarding the publication of this article.

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References.

1. Justiz Vaillant AA, Jamal Z, Ramphul K. Immunoglobulin. 2020 Aug 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 30035936.
2. Pisetsky, D.S., Buyon, J.P. and Manzi, S., Chapter 17. "Systemic lupus erythematosus". In: J.H. Klippel, L.J. Crofford, J.H. Stone, & C.M. Weyand. Primer on the Rheumatic Diseases. Edition 12. Arthritis Foundation, Atlanta, GA., 2001.
3. V. Rus, A. Hajeer, & M.C. Hochberg. Chapter 7. "Systemic lupus erythematosus". In: A.J. Silman, & M.C. Hochberg (eds). Epidemiology of the Rheumatic Disease. 2nd edition. Oxford University Press, New York, 2001.
4. R.C. Lawrence, D.T. Felson, C.G. Helmick, L.M. Arnold, H. Choi, R.A. Deyo, S. Gabriel, et al. For the National Arthritis Data Workgroup. "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II", Arthritis. Rheum. 58 (2008) 26-35. doi: 10.1002/art.23176.
5. C.G. Helmick, D.T. Felson, R.C. Lawrence, S. Gabriel, R. Hirsch, C.K. Kwoh, M.H. Liang, et al. For the National Arthritis Data Workgroup. "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I", Arthritis. Rheum. 58 (2008) 15-25. doi: 10.1002/art.23177.
6. J. Bayry J, V.S. Negi, S.V. Kaveri. Intravenous immunoglobulin therapy in rheumatic diseases. Nat. Rev. Rheumatol. 7 (2011) 349-59. doi: 10.1038/nrrheum.2011.61.
7. P.R. Timmerman. Intravenous immunoglobulin in oncology nursing practice. Oncol. Nurs. Forum. 20 (1993) 69-75.
8. R. Lemieux, R. Bazin, S. Néron. Therapeutic intravenous immunoglobulins. Mol. Immunol. 42 (2005) 839-48. doi: 10.1016/j.molimm.2004.07.046
9. T. Sapir, Y. Shoenfeld. Facing the enigma of immunomodulatory effects of intravenous immunoglobulin. Clin. Rev. Allergy. Immunol. 29 (2005) 185- 99. doi: 10.1385/CRIAI:29:3:185.
10. G. García-Guevara, R. Ríos-Corzo, A. Díaz-Mora, M. López-López, J. Hernández-Flores, H. Fragoso-Loyo, J. Ávila-Vázquez, et al. Pneumonia in patients with systemic lupus erythematosus: Epidemiology, microbiology and outcomes. Lupus. 27 (2018) 1953-1959. doi: 10.1177/0961203318799207.
11. Nobee A, Justiz Vaillant A, Akpaka PE, Poon-King P. Levels of Interleukin 17 and 23 in Patients with Systemic Lupus Erythematosus (SLE) in Trinidad and Tobago. Journal of Immunochemistry & Immunopathology 2016, 2: 115.

12. Justiz Vaillant A. A Female With Systemic Lupus Erythematosus and Streptococcal Pneumonia Treated With Intravenous Immunoglobulins (Ivig). Preprints.org; 2020. DOI: 10.20944/preprints202009.0544.v1.
13. Vaillant AAJ, Ramirez N, Cadiz A, Akpaka PE (2013) Case Reports on the Use of Intravenous Immunoglobulins (IVIG) in the Treatment of Systemic Lupus Erythematosus (SLE). J Clin Case Rep 3: 263. doi:10.4172/2165-7920.1000263
14. Justiz Vaillant AA, Jan A. Physiology, Immune Response. [Up-dated 2019 Mar 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-.
15. Justiz Vaillant A, Akpaka PE, and Poon-King P. Systemic Lupus Erythematosus: Some Epidemiological and Clinical Aspects." American Journal of Public Health Research 2015, 3 (2): 46-50.
16. Justiz Vaillant A. A Female with Systemic Lupus Erythematosus and Streptococcal Pneumonia Treated with Intravenous Immunoglobulins (Ivig). Preprints.org; 2020. DOI: 10.20944/preprints202009.0544.v1.
17. Justiz Vaillant AA, Varacallo M. Acute Lupus Erythematosus. [Up-dated 2019 Mar 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-.
18. Imbach P. Treatment of immune thrombocytopenia with intravenous immunoglobulin and insights for other diseases. A historical review. Swiss Med Wkly. 2012 May 31;142:w13593.
19. Sibéril S, Elluru S, Negi VS, Ephrem A, Misra N, Delignat S, Bayary J, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV. Intravenous immunoglobulin in autoimmune and inflammatory diseases: more than mere transfer of antibodies. Transfus Apher Sci. 2007 Aug;37(1):103-7.
20. Sapir T, Blank M, Shoenfeld Y. Immunomodulatory effects of intravenous immunoglobulins as a treatment for autoimmune diseases, cancer, and recurrent pregnancy loss. Ann N Y Acad Sci. 2005 Jun;1051:743-78.
21. Mouthon L, Berezné A, Le Guern V, Guillevin L. Intravenous immunoglobulins: therapeutic indications. Presse Med. 2005 Sep 24; 34(16 Pt 1):1166-75.
22. Feasby T, Banwell B, Benstead T, Bril V, Brouwers M, Freedman M, Hahn A, Hume H, Freedman J, Pi D, Wadsworth L. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev. 2007 Apr; 21(2 Suppl 1):S57-107.
23. Toubi E, Kessel A, Shoenfeld Y. High-dose intravenous immunoglobulins: an option in the treatment of systemic lupus erythematosus. Hum Immunol. 2005 Apr;66(4):395-402.
24. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008 Jan;58(1):15-25.
25. Elliott C, Justiz-Vaillant A. Nosocomial Infections: A 360-degree Review.

International Biological and Biomedical Journal. 2018 Mar 10;4(2):72-81.

26. Justiz Vaillant AA, Qurie A. Immunodeficiency. 2020 Aug 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 29763203.
27. Galeotti C, Maddur MS, Kazatchkine MD, Mouthon L, Kaveri SV. Intravenous immunoglobulins in autoimmune and inflammatory disorders: beyond a simple substitution. Transfus Clin Biol. 2009 May;16(2):75-9.
28. Lemieux R, Bazin R, Néron S. Therapeutic intravenous immunoglobulins. Mol Immunol. 2005 May; 42 (7): 839-48.
29. Rossi F, Dietrich G, Kazatchkine MD. Anti-idiotypes against autoantibodies in normal immunoglobulins: evidence for network regulation of human autoimmune responses. Immunol Rev. 1989 Aug;110:135-49.
30. Lacroix-Desmazes S, Mouthon L, Spalter SH, Kaveri S, Kazatchkine MD. Immunoglobulins and the regulation of autoimmunity through the immune network. Clin Exp Rheumatol. 1996 May-Jun;14 Suppl 15:S9-15.
31. Dietrich G, Kaveri SV, Kazatchkine MD. Modulation of autoimmunity by intravenous immune globulin through interaction with the function of the immune/idiotypic network. Clin Immunol Immunopathol. 1992 Jan;62(1 Pt 2):S73-81.
32. C, Desai R, Kazatchkine MD. Mechanisms of action of intravenous immune globulin in immune-mediated diseases. Clin Exp Immunol. 1996 May;104 Suppl 1:3-9.
33. Lacroix-Desmazes S, Kaveri S, Kazatchkine MD. Regulation of autoreactivity by the idiotypic network and therapeutic modulation of autoimmunity by polyvalent intravenous immunoglobulins (IgIV). Rev Neurol (Paris). 1996 May;152(5):349-54.
34. Hurez V, Kaveri SV, Kazatchkine MD. Normal polyspecific immunoglobulin G (IVIg) in the treatment of autoimmune diseases. J Autoimmun. 1993 Dec; 6(6):675-81.
35. Guilpain P, Chanseaud Y, Tamby MC, Larroche C, Guillevin L, Kaveri SV, Kazatchkine MD, Mouthon L. Immunomodulatory effects of intravenous immunoglobulins. Presse Med. 2004 Oct 9;33(17):1183-94.
36. Negi VS, Elluru S, Sibéril S, Graff-Dubois S, Mouthon L, Kazatchkine MD, Lacroix-Desmazes S, Bayry J, Kaveri SV. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. J Clin Immunol. 2007 May;27(3):233-45.
37. Sapir T, Shoenfeld Y. Facing the enigma of immunomodulatory effects of intravenous immunoglobulin. Clin Rev Allergy Immunol.2005 Dec;29(3):185-99.
38. Mouthon L, Kaveri SV, Spalter SH, Lacroix-Desmazes S, Lefranc C, Desai R, Kazatchkine MD. Mechanisms of action of intravenous immune globulin in immune-mediated diseases. Clin Exp Immunol. 1996 May;104 Suppl 1:3-9.
39. Mouthon L, Bussone G, Kaveri S. Indications and mechanisms of action of the intravenous immunoglobulines in the systemic autoimmune and inflammatory pathologies. Rev Med Interne. 2009 Dec; 30(12 Suppl):H14-20.

40. Ballow M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. J Allergy Clin Immunol. 2011 Feb;127(2):315-23; quiz 324-5.
41. Kazatchkine M, Mouthon L, Kaveri SV. Immunomodulatory effects of intravenous immunoglobulins. Ann Med Interne (Paris). 2000 May;151 Suppl 1:1S13-8.
42. Bayry J, Misra N, Latry V, Prost F, Delignat S, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV. Mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. Transfus Clin Biol. 2003;10(3):165-9.
43. Ibáñez C, Montoro-Ronsano JB. Intravenous immunoglobulin preparations and autoimmune disorders: mechanisms of action. Curr Pharm Biotechnol. 2003 Aug;4(4):239-47.
44. Emmi L, Chiarini F. The role of intravenous immunoglobulin therapy in autoimmune and inflammatory disorders. Neurol Sci. 2002 Apr;23 Suppl 1:S1-8.
45. Justiz Vaillant AA, Nessel TA, Zito PM. Immunotherapy. 2020 Sep 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 30085588.
46. Justiz Vaillant AA, Qurie A. Interleukin. 2020 Aug 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 29763015.