

## Case Reports on the Use of Intravenous Immunoglobulins (IVIG) in the Treatment of Systemic Lupus Erythematosus (SLE)

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### Abstract

**Introduction:** This work represents a preliminary study of the treatment of systemic lupus erythematosus with a commercially available intravenous immunoglobulin. The aim of this study was to assess the efficacy of this product in three patients aged 16, 34 and 49 diagnosed with systemic lupus erythematosus at the Internal Medicine Service of "Freire de Andrade" Hospital, Cuba.

**Case report summary:** The patients had a history of treatment with several drugs, including immune-suppressants. However recurrent respiratory tract infections, skin rash as well as several immunological abnormalities were present. Intravenous immunoglobulin (5-10 g/day) was given intravenously during five consecutive days, in the absence of other types of immunotherapy. An immunological profile before and after the intravenous immunoglobulin therapy was performed. In addition the patients were clinically evaluated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. The intravenous immunoglobulin therapy was highly effective in all patients due to its immunosuppressive, anti-inflammatory, immunomodulating and antimicrobial properties. It also prevented some of the frequent complications associated with the traditional immunotherapy in systemic lupus erythematosus.

**Conclusion:** We recommend new clinical studies on large group of patients to establish the efficacy and side effects of intravenous immunoglobulin as a first line therapy in systemic lupus erythematosus.

**Keywords:** Intravenous immunoglobulins; Systemic lupus erythematosus; IgG

### Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease of unknown origin in which various immunological factors are implicated. It affects different organs and tissues and its complications are often life-threatening [1]. Autoantibodies are produced against nuclear and cytoplasmic auto-antigens. Immunoglobulins and complement components are deposited along glomerular basement membrane and at the dermal-epidermal junction [1,2]. The evolution of SLE is uncertain and alternates remissions with relapses. Treatment includes glucocorticoids to which a number of patients do not respond to adequately in addition to their side effects, cytostatic and anti-malarial agents, immunomodulators, antibiotics and non-steroid anti-inflammatory drugs [1,2].

The successful use of intravenous immunoglobulins in autoimmune disorders has been cited by several authors [3]. IVIG has been used to treat two cases with lupus nephritis, reducing the proteinuria and decreasing the pathogenic anti-dsDNA antibodies [4]. Two cases of refractory SLE were successfully treated with IVIG that provoked the immediate recovery from severe pancytopenia and the improvement of proteinuria [5]. IVIG has been used successfully in a 23-year-old woman with SLE, admitted because of severe psychosis manifested by depression, delusions and inability to perform minimal daily activities [6]. It was reported an unusual case of elderly-onset systemic lupus erythematosus in a woman initially diagnosed with discoid lupus, and subsequently admitted to hospital due to a progressive psycho-motor deficit. Electrophysiological measurements suggested a diagnosis of acute motor sensory axonal neuropathy and she died despite the use of IVIG [7].

The IVIG used is a commercially available product, manufactured in Cuba in the Center of Hemoderivatives, Havana city from pooled IgG of thousand blood donors. It has proved its efficacy as an IVIG in the treatment of five patients with autoimmune diseases three of which we report in this paper. It contains highly purified IgG molecules

with a wide spectrum of specificities, which mediate complement activation, opsonization, neutralization and other biological activities. This IVIG has few side effects. Beneficial effects of IVIG therapy in SLE patients were evaluated utilizing the Systemic lupus erythematosus disease activity index (SLEDAI) score [8] and that was evaluated by a rheumatologist. Active SLE disease was defined as a SLEDAI score of  $\geq 3$  or 4 and inactive SLE disease was defined as a SLEDAI score of  $<3$  [4]. The aim of this study was to report on the efficacy of the IVIG therapy in 3 patients with active SLE, admitted at the "Internal Medicine Service of Freire de Andrade" Hospital, Havana Cuba.

### Summary of Case Report 1

A 16 year-old Hispanic white female was admitted to the hospital with symptoms of disorientation and malaise. She was well until a couple of weeks prior to presentation to the hospital when she developed weight loss, polyarthralgia, headache, skin manifestations and other complaints. She was a well-known case of SLE and she was treated in the past with corticosteroids, non-steroid anti-inflammatory drugs and immune-suppressants. Her physical examination revealed that she was febrile and hypertensive. She had skin lesions including the classic "butterfly rash" and vasculitis; signs of pleurisy and pericardial friction rub, the echocardiography showed a moderate-sized pericardial effusion. Laboratory findings included anemia, leucopenia,

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proteinuria, high sedimentation rate, elevated serum C-reactive protein concentration, low levels of C3 and decreased activity of total hemolytic complement, positive Antinuclear Antibodies (ANA) and the presence of anti-dsDNA antibodies. Chest X-rays revealed features of pericarditis, pleural effusion and bronchopneumonia. The patient was transferred to the intensive care unit where she was treated with 10 g/day of IVIG for 5 consecutive days. There was a marked clinical improvement after completion of the immunotherapy with IVIG. There was an improvement in the skin, pulmonary and cardiovascular problems. Laboratory findings showed an increase in the activity of the hemolytic complement, lower titer of anti-dsDNA and red blood cell antibodies. A chest X-ray showed a resolution of the pleurisy and lower respiratory tract infection. The patient was transferred to the Internal Medicine ward, where she was observed for a further 72 hours before she was discharged home. She was able to perform her normal activities without assistance. She was further treated with 10 g/month of IVIG therapy. A clinical and humoral remission of SLE was observed for a period of a year. The SLEDAI score before and after the treatment with IVIG was 21 and <3 respectively.

### Summary of Case Report 2

A 49 year-old Hispanic white male was admitted to the hospital. The patient reported that he was exposed to sunlight on a daily basis at his workplace (seaport). He was placed on prednisone but was non-compliant. He also complained of marked asthenia, anorexia and weight loss. His physical examination revealed several skin lesions including “butterfly rash”, erythematous plaques and papules; extensive oropharyngeal ulcers, alopecia and vasculitis. Other positive clinical data were polyarthritides and hyperreflexia. His immunological profile showed low C3 levels, positive antinuclear antibodies, anti-dsDNA antibodies, leucopenia, impaired cellular immunity, false positive Venereal Disease Research Laboratory (VDRL) and positive Coombs’ test. Five (5) g/day of IVIG was administered for 5 consecutive days. After the third dosage of the IVIG a marked clinical improvement was observed. Abnormal laboratory findings resolved. The patient was followed in the out-patient rheumatology and immunology clinic for a period of a year without clinical and humoral exacerbation of SLE (a SLEDAI score of <3). He was further treated with 10 g of IVIG monthly. No further complications were observed. The SLEDAI score before and after the treatment was 21 and 2 respectively.

### Summary of Case Report 3

A 34 year-old Hispanic white male presented with history of weakness, depression, generalized skin rash, angioneurotic edema, recurrent respiratory tract infections and arthritis. He was suspected to have SLE by his family doctor, who previously had treated him with prednisone, non-steroid anti-inflammatory drugs and antibiotics without complete remission of his disease. On admission laboratory findings were anaemia, increased circulating immunocomplexes, decreased C3, hypergammaglobulinemia, positive Coombs’ test, presence of anti-nuclear antibodies and positive anti-dsDNA antibodies. A chest X-ray revealed a discrete right pleural effusion. It was decided to treat the patient with 5 g/day of IVIG for 5 consecutive days. After treatment the most important findings were remission of the vasculitis and polyarthritides. There was an important remission of humoral findings such as C3, and C4 after completion of the treatment. The patient was further treated with 10 g/month of IVIG and no further SLE crisis was observed in one year of evaluation, except for an intermittent episode of upper respiratory tract infection without major consequences. The SLEDAI score before treatment was 18, which was

a severe flare, and after treatment with IVIG the score was less than 3.

### Discussion

The treatment with IVIG was effective for the management of the lupus crisis in these 3 patients in dosage of 5-10 g/day for 5 consecutive days, and then 10 g monthly for a year. Beneficial effects of IVIG therapy in SLE patients were proved through decrease of SLEDAI score decrease. IVIG was effective for the clearance of most skin lesions. The frequently used dose of IVIG is 0.4 g/Kg/d but we used a low dose based on our previous experience of other SLE cases that we successfully treated with low dose IVIG only. The first case in this study required a higher immunoglobulin dose because she suffered acute pericarditis [9]. Other authors have reported the beneficial use of high doses of IVIG in the treatment of SLE with skin problems such as vasculitis and “butterfly rash” [5]. Rarely, hematological (Coombs’ test positive hemolysis), neurological (aseptic meningitis) or renal (transient rises in serum creatinine) adverse effects may be seen when high doses of IVIG are used for immunomodulatory purposes. Hemolysis, due to passive transmission of blood group antibodies (anti-A, anti-D), may be prevented by selecting IVIG batches that give a negative cross-match between the recipient’s red cells and IVIG [10,11]. In addition the IVIG therapy was efficient for the management of the lower respiratory tract infections associated with SLE. This can be explained by the presence of antibodies directed against a wide spectrum of microorganisms including bacteria, viruses and fungi [12].

We hypothesize that the immune-suppressing activity of IVIG may be due to its capacity to inhibit the production of autoantibodies, probably by blocking immunoglobulin receptors on B cells. The IVIG therapy contains opsonins, which may improve the phagocytosis of immunocomplexes by antigen-presenting cells. The presence of anti-idiotypic antibodies in this IVIG plays an important role in the regulation of the immune response. In vitro studies have shown the capacity of the IVIG to inhibit the replication of Coxsackie A9 strain isolated from the cerebrospinal fluid of a patient with epidemic neuropathy [13].

The IVIG therapy could be used not only for immunodeficient patients, but also in patients with systemic lupus, because of its positive immunomodulatory effects in autoimmune and inflammatory disorders as well as minor side effects [14]. The IgG repertoire of IVIG is polyclonal, and contains self-reactive antibodies. IVIG contains antibodies directed against several molecules, for example CD4, CD8, HLA, cytokines, T and B cell receptors and heat-shock proteins. IVIG can proceed through direct interaction with immune cells or indirectly by binding to soluble messengers [15].

### Conclusion

We recommend new clinical studies on large group of patients to establish the efficacy and side effects of intravenous immunoglobulin as a first line therapy in systemic lupus erythematosus.

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