Abstract: This review covers the major advances in the therapeutic potential of intravenous immunoglobulin (IVIG) in systemic lupus erythematosus (SLE) published in Medline during the last years. IVIG is a potent biological drug, utilised in neuroimmunologic, infectious, dermatologic, haematologic, autoimmune, inflammatory and idiopathic disorders. Over the past two decades, IVIG has been utilised as adjunct therapy for various manifestations of SLE. IVIG may be particularly attractive for neurological involvement. Compared to immunosuppressive agents, IVIG may be advantageous due to its few and transient minor adverse effects.

Keywords: Autoimmune diseases, intravenous immunoglobulin (IVIG), systemic lupus erythematosus (SLE)

Introduction

Systemic lupus erythematosus (SLE) is a prototypic multisystem chronic autoimmune disease with various clinical and serological manifestations. The mechanisms arising to the development of lupus are still recondite, but are associated with excessive autoantibody production, aberrant clearance of apoptotic cells, with a genetic and hormonal influence. To date, the conventional therapy for severe disease is immunosuppressive but related to intolerable toxicities. Since SLE is a disease predominantly of women in the reproductive age, these medications are recently often refused. Hence, IVIG, harboring a good beneficial and safety profile, may be an appropriate therapy for certain patients. Here we review the indications for treatment, mechanisms of actions, beneficial and adverse effects of IVIG in SLE patients.

Intravenous immunoglobulin (IVIG), a widely-utilised biologic agent, is approved as a replacement treatment for immunodeficiency states and immunoglobulin deficiencies and is warranted for idiopathic thrombocytopenic purpura, Kawasaki’s disease, and dermatopolymyositis. Furthermore, IVIG has also been extensively administered as an adjunct therapy in various manifestations of SLE, Guillain-Barre syndrome, polyneuropathies, antiphospholipid syndrome (APS), myasthenia gravis (MG), scleroderma, and vasculitides such as Wegener granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa, and microscopic polyangiitis. Treatment with IVIG is indicated in lupus patients with concomitant infection, those where treatment with steroids or cytotoxic agents is contraindicated or refused, and who are resistant to conventional therapy.

Mechanisms of Action of IVIG

IVIG is an immunomodulatory agent capable of modulating SLE and other autoimmune disease in both human and animal
models. Mechanisms of action include Fc-receptor blockade, neutralisation of pathogenic autoantibodies via idiotype and anti-idiotypic antibodies, effects on the Fas apoptotic pathway via agonistic and antagonistic anti-Fas antibodies, regulation of complement components, modulation of cytokine secretion, hindrance of natural-killer cell activity, inhibition of matrix metalloproteinase-9, suppression of NFKB activation and IKB degradation, decrease in leukocyte recruitment, attenuation of T cell stimulation, effects on antibody kinetics, effects of dendritic cells, and neutralisation of B cell activating factor (BAFF) in B cell survival.21-25

Adverse Effects of IVIG

IVIG therapy is associated predominantly with mild and transient adverse effects (AE). The immediate AEs usually include: headache, flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnoea, back pain, nausea, vomiting, diarrhoea, blood pressure changes, tachycardia, and anaphylactic reactions especially in IgA-deficient patients.26 Immediate adverse effects appear early and in many cases, during the first 30 min of the infusion.27 Late AEs are rare and include acute renal failure, thrombo-embolic events, aseptic meningitis, neutropenia, autoimmune haemolytic anaemia, pseudo-hyponatraemia, skin reactions and rare events of arthritis.27 Patients with prior migraine may experience more severe and persistent headaches. For the most part, mild AEs are not an indication for the cessation of IVIG therapy, and many patients respond to adjustment of the infusion rate for a brief period. Pre-treatment with anti-inflammatory drugs, anti-histamines, or low-dose steroids have been recommended and may eliminate mild to moderate reactions.28 In our experience, IV hydrocortisone (100-200 mg) administered prior to the initiation of the IVIG course resulted in less immediate AE.

Acute renal failure is a severe AE, and occurs within hours to 5 days following IVIG therapy. It is usually oliguric, transient, and occurs mostly on using sucrose-containing products that may lead to osmotic injury.27,28 Some patients require haemodialysis, but the renal failure is usually completely reversible with a return to baseline creatinine within two weeks. IVIG should be considered a potentially nephrotoxic agent in patients at risk including those with diabetes mellitus, previous history of renal disease, dehydation, advanced age, hypertension, hyperviscosity and hence the utilisation of IVIG should be judicious.29 Product features affecting clinical tolerability including volume load, sugar and/or sodium content, osmolarity, and IgA content are all potential risk factors for patients with various co-morbidities.28

Thrombo-embolic complications in IVIG treated patients are a result of several factors: hyperviscosity (especially in the elderly with low cardiac output, patients with diabetes mellitus, those with a history of previous thrombo-embolic events and immobilised patients), hypertension, dyslipidaemia, or high dose IVIG administered at a rapid infusion rate.30 An increased risk of thrombo-embolic events in patients with SLE and secondary antiphospholipid syndrome (APS) has yet to be addressed. Severe anaphylactic reactions following IVIG administration are rare. IgA deficient patients may form macromolecular complexes with anti-IgA Ab of the recipient of IVIG that can lead to anaphylactic reaction. Anaphylaxis can be prevented by using IgA-depleted IVIG.31 Procedures that may reduce the AE include the appropriate selection of preparation and dose. One should consider decreasing the dose and/or infusion rate. Infusion surveillance and pre-medication are warranted.

Dose

In SLE and other autoimmune diseases, patients should receive a high-dose IVIG protocol. The dose is 2 gram/kg per course divided over a 5 day period (or 400 mg/kg/d). We recommend not to exceed a total of 140 gram per course in order to reduce the potential hyperviscosity AEs. Furthermore, we administer 100-200 mg of hydrocortisone intravenous before the initiation of the IVIG course (a single dose on the first day of IVIG therapy) to reduce immediate minor adverse events. IVIG should be administered at a slow infusion rate over a period of 8 hours (50 mg/min). Our protocol consists of monthly courses for 6 months, followed by repeated courses every 2-3 months. The total duration of treatment is yet to be established.

IVIG in Treatment of SLE

The various clinical manifestations of SLE reported to be successfully treated by IVIG in case reports include autoimmune haemolytic anaemia, acquired factor VIII
inhibitors, acquired von Willebrand disease, pure red cell aplasia, thrombocytopenia, pancytopenia, myelofibrosis, pneumonia, pleural effusion, pericarditis, myocarditis, cardiogenic shock, nephritis, end-stage renal disease, encephalitis, neuropsychiatric lupus, psychosis, peripheral neuropathy, polyradiculoneuropathy, and vasculitis. The most extensive experience is with lupus nephritis. There are only a few case series of IVIG use in patients with SLE with various manifestations, in which the response rate to IVIG therapy ranged from 33% to 100%.5

There is mounting evidence that SLE patients with diverse manifestations respond well to IVIG therapy.5 Reports of more than one case include pancytopenia (predominantly thrombocytopenia),5,32,33 psychosis,34-36 pleural effusion,37 cardiitis,38 vasculitis,39 and lupus nephritis. In most of those patients, an improvement in proteinuria and in kidney function was observed.29 However, due to the newer immunosuppressive drugs that are potent for lupus nephritis (mycophenolate mofetil, rituximab), IVIG should be utilised as salvage therapy for this indication. The beneficial effects of IVIG are usually prompt, with marked improvement within a few days for haematological manifestations such as haemolysis and thrombocytopenia. Improvement for renal and neuropsychiatric manifestation (particularly in those patients who were resistant to conventional therapies) may take longer. Clinical response usually has a limited duration of 3-4 weeks and is maintained by monthly infusions.2,40 The benefit can be associated with a reduction in anti-DNA titers, erythrocyte sedimentation rate (ESR) and an increase in levels of complement.

Open Trials

There are no randomised double blind studies on the effect of IVIG in SLE. Clinical studies are small series due to the rarity of the disease and individual indications for IVIG utilisation.

One study evaluated the clinical and serological effects of IVIG in 12 lupus patients with mild to moderate disease activity. IVIG was administered by the high-dose regimen, and a second dose was given 3 weeks later. IVIG was an adjunct therapy to the continuing conventional therapy including steroids. The response was very good for thrombocytopenia, rash, and arthritis. There was a decrease in disease activity measured by the SLAM index. The response was transient and the clinical improvement ceased after 5-6 weeks from the last infusion.39

Another open trial tested the effect of IVIG over a period of time. Progressive clinical improvement was assessed in 11 patients and an improvement in haematological manifestations and a reduction in ANA and ESR occurred (in contrast to the previous study).41

Another group evaluated the effect of IVIG during SLE flares (excluding nephritis) in 13 lupus patients. In all but one patient there was a reduction in the disease activity index by the fourth week. There was a good response to fever, myalgias, and arthritis.42

High-dose IVIG (2 gr/kg divided over 5 days) in monthly courses, for 1 to 8 treatment courses was administered in the largest study of 20 SLE patients. The age range was 21-53 years old with disease duration of 6.2 years. The indications for IVIG treatment were diverse and included thrombocytopenia, massive proteinuria, arthritis, fever, haemolytic or aplastic anaemia, arthralgia, mood changes and psychosis. Prior to IVIG treatment, 13 patients were treated with prednisone, 4 patients were treated with combined therapy (3-prednisone and cyclophosphamide, 1-prednisone and hydroxychloroquine, 1-hydroxychloroquine and 1-aspirin). IVIG had a steroid sparing effect in most of the patients. Among 15 patients whose daily prednisone doses were known, the decrease in dosage (mean±SD) was from 29.7±18.2 to 13.8±16.7 mg/day (p=0.02). In addition, a comparison of disease activity by the SLEDAI score in 9 patients evaluated before and after IVIG, revealed a decrease from 19±4.7 to 4±2.9 (p<0.0001) indicative of a significant improvement. IVIG treatment was found to be beneficial in 85% of the patients based on either disappearance or marked improvement of the main clinical manifestations.8

Renal Involvement

IVIG is beneficial for mild, moderate and severe lupus activity. The most experience is with renal involvement. Among 106 patients reported in the literature, IVIG was indicated predominantly for Class III-V determined by renal biopsy. In most reports proteinuria, nephritic syndrome, and creatinine clearance were improved. One randomised trial among 14
IVIG THERAPY IN SLE

patients with proliferative lupus nephritis demonstrated that monthly low-dose IVIG (400 mg/kg/course administered in one day) maintained remission over 18 months, similar to standard intravenous cyclophosphamide treatment. In a clinical trial of 116 patients with glomerulonephritis from any cause (including 58 SLE patients) IVIG was beneficial in 40 patients, but 12 developed end-stage renal disease. The dosage and number of courses were variable. Most of the patients that developed nephrotoxicity received sucrose-containing preparations. Mortality occurred in 10-15% of cases.

Haematological Involvement

IVIG is beneficial for many haematological aspects of SLE including autoimmune haemolytic anaemia, acquired factor VIII inhibitors, acquired von Willebrand disease, pure red cell aplasia, thrombocytopenia, and pancytopenia based on sporadic reports. The aim of a recent study was to evaluate the response to treatment and the long-term outcome in a cohort of 26 lupus patients in whom severe autoimmune haemolytic anaemia (AHA) was the major manifestation. The patients were initially treated with corticosteroids. Only three patients experienced multiple relapses despite splenectomy and several immunosuppressants. IVIG induced transient response in three cases. These results are similar to previously reported sporadic reports.

Two cases of TTP presented during rapidly progressive lupus nephritis, with grand-mal seizures, thrombocytopenia and microangiopathic haemolytic anaemia. Both cases were treated with haemodialysis, plasma exchange, corticosteroids, cyclophosphamide and IVIG. In both cases the TTP was improved but not the renal function. It is yet to be determined the beneficial effect of IVIG in this setting.

Serositis and Myocarditis

IVIG is beneficial for serositis which was reported in lupus patients with other major organ involvement. The response was maintained and other immunosuppressive drugs could be discontinued. IVIG was also a successful modality in a case report for lupus myocarditis. The response was rapid with a normalisation of the ejection fraction that was maintained.

Cutaneous Involvement

IVIG is utilised for blistering autoimmune dermatological diseases. In one open series, 7 of 11 lupus patients with refractory cutaneous involvement had a beneficial response to IVIG given at a high dose initially and low-dose subsequently over a period of 6 months.

Neurological Involvement

IVIG is beneficial for polyneuropathies that can also be found in lupus including Guillain-Barre syndrome, vasculitic polyneuropathy, and chronic inflammatory demyelinating polyneuropathy (CIDP). CIDP is an uncommon, but not rare, manifestation of SLE. In a recent report of 6 patients with SLE and CIDP, 3 (50%) achieved a substantial clinical response to IVIG and the remainder had a minimal response. Certain characteristics including early CIDP diagnosis, involvement of all 4 extremities, hyporeflexia of the upper extremities, and slowed motor nerve conduction velocity of the median nerve in addition to SLE involvement of critical internal organs and the presence of multiple antibodies associated with SLE all predicted a good response to IVIG. The improved patients were more likely to have received treatment earlier (within 1 year of CIDP onset) and to respond faster (<1 to 3 months) than minimally improved patients.

There are only a few anecdotal reports on the beneficial effect of IVIG in CNS lupus. High-dose IVIG was beneficial in 2 patients with psychosis and a patient with encephalitis. In a recent case report the acute onset of symptoms of depression, mania, and psychosis and their complete resolution 48 h following a 5-day treatment course of IVIG in a 20-year-old woman with SLE was described.

Our group determined an improvement in chronic cognitive deficit, as the major manifestation of neuropsychiatric SLE in 4 patients, following repeated courses of high-dose IVIG. Neuropsychiatric lupus was diagnosed as a composite of clinical manifestations, abnormal brain MRI and SPECT scans, abnormal neuropsychological testing, in the setting of active lupus by serology. Patients received at least 6 monthly courses of IVIG. Subjective improvement occurred within 3 months of therapy.
Recently, a case of a 33-year-old woman with SLE who developed chorea with multiple involuntary movements and cognitive disturbances was described. Because the methylprednisolone therapy administered appeared to lead to Salmonella enteritidis infection, IVIG in a total dose 100 g was administered after which a remarkable improvement of the abnormal movements and cognitive function was noted within 7 days. In this case due to the combination of severe lupus and concomitant infection, IVIG became the treatment of choice.49

We have recently evaluated the long-term effect of IVIG in SLE patients. Patients were recruited from the Lupus and Rheumatology Clinic over a 5 year period. Eleven SLE patients were treated with a high dose IVIG protocol: 2 gr/kg over a 5 day period once a month for 6 months, followed by therapy every 2-3 months. Most courses were preceded by a single hydrocortisone 100-200 mg IV dose to prevent side effects. A significant decrease in the SLEDAI score indicating partial or complete remission was demonstrated. Mild and transient adverse effects (headache, fatigue and nausea) were present in 50% of patients and persisted with long-term therapy. The severe adverse effects, which appeared in two patients with SLE and secondary APS during short term therapy, were pulmonary embolism and seizures. In patients who responded to therapy, IVIG harbored a significant steroid sparing effect. A beneficial effect and a good safety profile were maintained with long term high-dose IVIG therapy for SLE patients. Long term remissions were sustained.50

Conclusions

We suggest that IVIG devoid of sucrose, at a dose of 2 g/kg over a 5-d period given uniformly and at a slow infusion rate in patients without an increased risk for thromboembolic events or renal failure, is a safe and beneficial adjunct therapy for SLE patients who are resistant to or refuse conventional treatment. IVIG may be beneficial for an array of haematological and neurological manifestations in lupus and should be further investigated. The duration of therapy is yet to be established. Controlled trials are warranted.

References


