Low Dose Intravenous Immunoglobulin in Systemic Lupus Erythematosus: Analysis of 62 Cases

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Abstract

Background: Systemic lupus erythematosus is an autoimmune disease with diverse clinical manifestations that cannot always be regulated by steroids and immunosuppressive therapy. Intravenous immunoglobulin is an optional immunomodulatory agent for the treatment of SLE, but the appropriate indications for its use, duration of therapy and recommended dosage are yet to be established. In SLE patients, most publications report the utilization of a high dose (2 g/kg body weight) protocol.

Objectives: To investigate whether lower doses of IVIg are beneficial for SLE patients.

Methods: We retrospectively analyzed the medical records of 62 patients who received low dose IVIg (approximately 0.5 g/kg body weight).

Results: The treatment was associated with clinical improvement in many specific disease manifestations, along with a continuous decrease in SLEDAI scores (SLE Disease Activity Index). However, thrombocytopenia, alopecia and vasculitis did not improve following IVIg therapy.

Conclusions: Low dose IVIg is a possible therapeutic option in SLE and is associated with lower cost than the high dose regimen and possibly fewer adverse effects.

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Intravenous immunoglobulin therapy was originally utilized for the treatment of various immunodeficiency states [1]. To date, IVIg is a standard therapeutic modality for certain autoimmune diseases, including immune thrombocytopenic purpura, Kawasaki disease, Guillain-Barré syndrome and polymyositis, where it is used as an immunomodulatory agent [1]. IVIg is also occasionally used for the treatment of systemic lupus erythematosus, but for this indication it is still considered experimental and without any clear indications and methods of use [2,3]. Many case reports and case series (usually small) have described the beneficial effect of IVIg in SLE [4-14]. In general, IVIg therapy was well tolerated and resulted in better outcome, as measured by response of specific clinical manifestations and disease activity indexes, and it also had a steroid-sparing effect in some reports [14]. Most of the above-mentioned reports described a high dose protocol (2 g/kg body weight divided over 5 days), considered the immunomodulatory dose of IVIg. As IVIg therapy is expensive and is associated with adverse effects [15-18], we aimed to investigate whether lower doses of IVIg are beneficial for SLE patients. We analyzed the medical records of 62 SLE patients treated with low dose IVIg.

Patients and Methods

This retrospective study included a review of the medical records of 62 patients who were diagnosed as having SLE based on at least four American College of Rheumatology criteria [19]. All were treated with low dose IVIg for various indications at different time points. The demographic data collected for every patient included age, gender, age at diagnosis of SLE, and age at the commencement of IVIg therapy. The data recorded on IVIg therapy included: IVIg dosage in the first treatment course, IVIg dosage in the subsequent courses, the interval between treatment courses, and total number of courses. Response to treatment was evaluated by using both the response to single specific manifestations of the disease, as well as evaluation of the SLE disease activity index score at several time points.

Results

Of the 62 patients included in the study, 7 were men. The patients' mean age at diagnosis was 33 ± 15 years and their mean age at the beginning of treatment was 40 ± 15 years. The dosage of IVIg used for the treatment of these SLE patients was variable but was approximately 0.5 g/kg body weight. IVIg dosage in the first course was 36 ± 18 g, IVIg dosage in the subsequent courses was 38 ± 42 g. The interval between treatment courses was 5 ± 2 weeks, and the number of treatment courses was 6 ± 6.

Regarding the clinical response to the treatment, Table 1 summarizes the precise rates of disappearance of specific clinical and laboratory manifestations of SLE. In general, mucosal ulcers,

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SLE = systemic lupus erythematosus

IVIg = intravenous immunoglobulin

Table 1. Response rate of specific disease manifestations of 62 SLE patients treated with low dose IVIg

Manifestation	Response rate (%)
Mucosal ulcers	100%
Fever	93%
Urinary casts	88%
New rash	75%
Pleurisy	71%
Pericarditis	60%
Hematuria	57%
Leukopenia	43%
Arthritis	30%
Low complement levels	27%
Proteinuria	20%
Headache	17%

Percentages represent patients in whom the abnormal clinical/laboratory abnormality completely resolved.

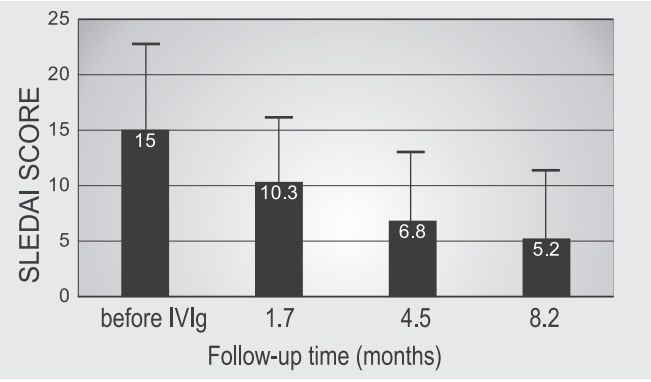

Figure 1. SLEDAI scores of 62 SLE patients treated with low dose IVIg before and at three different time points after the treatment

fever, urinary casts, new rash, hematuria, pericarditis and pleurisy resolved in more than 50% of the affected patients, along with disappearance of seizures and psychosis in two patients. On the other hand, leukopenia, arthritis, low complement levels, proteinuria and headache resolved in less than 50% of the affected patients. A few clinical manifestations did not improve at all following low dose IVIg: namely, thrombocytopenia (4 patients), vasculitis (6 patients) and alopecia (3 patients). A comparison of SLEDA scores before low dose IVIg therapy and at three different time points after IVIg administration (up to 8 months following therapy) disclosed a significant and continuous decline in the scores from 15 ± 7.8 to 5.2 ± 5.7 [Figure 1].

Discussion

IVIg has been widely reported as a possible immunomodulatory agent for SLE [4-14], mainly for severe cases in which it was considered as a salvage immunotherapeutic agent, but also as an add-on therapy for the disease. We previously reported that IVIg can reduce disease activity and daily prednisone dosages among SLE patients, as well as the autoantibodies associated with lupus [11]. Moreover, IVIg can also effectively ameliorate lupus nephritis in some cases [10], and has been reported to be as effective as cyclophosphamide in maintenance of lupus nephritis remission over 18 months [20]. The mechanisms of action of IVIg in autoimmune diseases are diverse and include all arms of the immune system. Anti-idiotypic antibodies within IVIg directed towards pathogenic idiotypes that are found over autoantibodies are also implicated in these mechanisms of action of IVIg [21,22]. Accordingly, it has been demonstrated that IVIg preparations enriched with anti-idiotypes against anti-dsDNA antibodies are much more effective in amelioration of experimental SLE compared to regular IVIg preparations [21]. Two recently reported mechanisms of action of IVIg include presence of anti-BAFF antibodies within IVIg preparations, and greater activity of T regulatory cells following IVIg infusion [23,24].

The role of the appropriate IVIg dosage for use in SLE patients, the indications for IVIg and the recommended duration of therapy has not been established, probably due to the rarity of the disease. There are almost no controlled studies on IVIg therapy in lupus, and most are anecdotal or observational studies. In this retrospective study, including 62 cases of SLE patients treated with IVIg, it seems that IVIg at a dose close to 0.5 g/kg body weight per therapeutic course can also be effective in the majority of cases. Most clinical manifestations of the disease have shown a significant response to the IVIg infusion, and, most important, an improvement in SLEDAI score was noted months after initiation of IVIg administration. The use of low dose IVIg, which is about one-quarter of the regular dosage usually used for immunomodulation (2 g/kg body weight), is preferred in terms of both cost and adverse effects. Although IVIg is relatively safe, few complications may accompany its usage, the most frequent being rashes, headaches and arthralgias, as well as more rare conditions such as aseptic meningitis, renal failure and thrombosis [15,16,18]. Another issue is the appropriate IVIg dosage for the treatment of patients with autoimmune diseases in general, and lupus in particular. One study reported a better therapeutic effect in Kawasaki disease using a high dose (2 g/kg) of IVIg than with a low dose (1 g/kg) of IVIg therapy [25]. However, a conclusion from one disease cannot necessarily be applied to another.

In this study we observed several manifestations that failed to respond to IVIg therapy in SLE, including thrombocytopenia, alopecia and vasculitis. In addition, an important manifestation of the disease, proteinuria, disappeared in only a few cases. Therefore, while use of low dose IVIg in SLE seems to be beneficial as an add-on therapy, there are still many unanswered questions, such as the appropriate dosage to be used in certain clinical manifestations and the required duration of treatment. Additional research is required to clarify these issues, and they should include comparative studies of low dose and high dose IVIg as well as a comparison of IVIg with other therapeutic agents in SLE patients who have a similar disease. This large retrospec-

SLEDAI = SLE Disease Activity Index

tive case series of 62 SLE patients treated successfully with low dose IVIg, a treatment that was associated with improved disease activity, provides new data to support the utilization of low dose IVIg in SLE.

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