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Role of intravenous immunoglobulins in the management of systemic lupus erythematosus: a single-centre experience

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ABSTRACT

Objectives Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown aetiology that can affect almost any organ in the body. Although there are no specific guidelines for the use of intravenous immunoglobulin (IG) in the treatment of patients with SLE, it is thought to be an effective treatment. Our study aimed to evaluate the effectiveness and safety of intravenous IG and to describe the possible profile of patients with SLE who are candidates for intravenous IG treatment.

Methods This study was designed to retrospectively analyse patients with SLE treated with 2 g/kg/month of intravenous IG (divided across 5 consecutive days). We collected demographic, clinical, laboratory and treatment data from the patient files. The side effects of the intravenous IG treatment, changes in the immunosuppressive therapy used and changes in the clinical and laboratory parameters after the intravenous IG treatment were evaluated.

Results This study included 31 patients with SLE. The main indication for intravenous IG treatment was haematological involvement (20, 64.5%) and thrombocytopenia in particular (8, 25.8%). Intravenous IG was initiated mainly for refractory disease. At the end of the treatment, the acute phase values, proteinuria, complement levels and anti-double-stranded DNA decreased significantly ($p<0.001$). In most cases, the side effects were mild and usually manifested as myalgia or a fever.

Conclusion Despite its high cost, intravenous IG has demonstrated effectiveness in treating refractory SLE, especially when there is haematological involvement. Specific clinical features at baseline may identify the patients who are more likely to respond to this therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Researchers have suggested the use of intravenous immunoglobulin (IG) for the treatment of autoimmune/inflammatory conditions and infections.

⇒ In many clinical aspects of systemic lupus erythematosus (SLE), intravenous IG is considered effective, despite the lack of published guidelines for the ideal dose, duration of treatment or subset of patients who are more likely to benefit from it.

WHAT THIS STUDY ADDS

⇒ This study allowed for the evaluation of post-treatment laboratory parameters and clinical findings in patients with SLE treated with intravenous IG.

⇒ Our study confirmed the efficacy of intravenous IG therapy in patients with SLE with treatment-resistant disease or contraindications to standard drugs.

⇒ It also provides insights into the clinical and laboratory characteristics of patients most likely to respond to treatment and those most likely to relapse after stopping treatment.

⇒ When evaluated in terms of side effects, it was shown that the side effect rate of the intravenous IG treatment was quite low and the side effects were mostly mild.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We believe that it is essential to find characteristics that indicate the treatment response and, consequently, choose the best candidates for intravenous IG, considering how expensive the procedure is.

⇒ This study highlights the need for further studies involving larger groups to confirm these findings and understand the effects of intravenous IG on patients with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, potentially life-threatening, multisystem, immune-mediated disorder. Patients may present with a wide array of symptoms, signs and laboratory findings, and they may have a variable prognosis that depends on the disease severity and the type of organ involvement.[1] The goals of therapy for patients with SLE are to achieve remission or low disease activity, prevent organ damage, minimise drug toxicity and improve quality of life.[2] The choice of drug therapy for SLE is highly individual and depends on the predominant symptoms, organ involvement, response to

previous therapy, disease activity, disease severity and developing complications.[3]

Intravenous immunoglobulin (IG) is made from combined donor IgG preparations and contains antibodies against a variety of foreign and self-antigens in addition to a wide range of infections.[4] The exact mechanism of action is unknown, but there are a number of immune-related effects that could be involved, such as the inhibition of the activation of B cells and dendritic cells, a reduction in the migration of inflammatory cells in muscle fibres, the downregulation of transforming growth factor-beta (TGFβ) expression in the muscle, the activation of regulatory T cells or the modulation of various cytokines.[5] A working group monograph of the American Academy of Allergy, Asthma and Immunology recommended the use of intravenous IG in immunodeficiency states (primary and secondary), neuroimmunological disorders, autoimmune/inflammatory conditions, infections and infection-related disorders and alloimmune processes.[6]

The effectiveness of intravenous IG treatment was determined in a study that included a small number of patients diagnosed with SLE and in a cohort of patients diagnosed with SLE who were followed for a long time.[7 8] In many clinical aspects of SLE, this treatment is deemed effective, despite the absence of published guidelines for the ideal dose of intravenous IG, the duration of treatment or the subset of patients who could benefit more from it.[9]

In this study, we aimed to retrospectively analyse the efficacy of intravenous IG in patients with SLE followed in a tertiary centre to determine the efficacy of the treatment, its possible side effects and a possible profile of the patients who are most likely to respond to this treatment.

SUBJECTS AND METHODS

Study design and sampling

This study was designed as a cross-sectional and retrospective study conducted in a single centre. 34 patients with SLE who were initially diagnosed and receiving high-dose intravenous IG therapy were included in this study, but five patients who did not attend the follow-up were excluded. A total of 31 patients who were regularly followed up at a tertiary rheumatology centre between November 2016 and January 2024 were included in the analyses. The patients diagnosed with SLE between 2016 and 2019 fulfilled the Systemic Lupus International Collaborating Clinics criteria, while the patients diagnosed with SLE in 2019 and later met the 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria.[10 11] The revised Sapporo antiphospholipid syndrome (APS) classification criteria (also known as the Sydney criteria) were used to identify patients with APS.[12]

At the onset of the disease, each patient was treated according to international guideline recommendations. Glucocorticoids, alone or in combination with one or more immunosuppressant drugs, were administered. All the patients included in the study received an intravenous IG infusion at a dose of 2 g/kg/month (divided across 5 consecutive days) at least once and up to six times. The intravenous IG treatment was added when the standard treatment failed to provide disease control or was contraindicated. Patients with overlap syndrome together with SLE, patients diagnosed with drug-related SLE and primary APS patients were excluded from the study.

Data collection

The demographic data, clinical findings, laboratory results, imaging findings and treatment methods of the patients were obtained from the patient files. The demographic data and clinical findings of the patients included the gender, age, age at the time of disease onset, disease duration at the onset of treatment, remission status, disease activity level, constitutional symptoms, neurological involvement, myalgia, oral aphthae, dry mouth, dry eyes, petechiae, purpura, joint involvement, Raynaud phenomenon, skin rashes and serous involvement (pleural effusion, pericardial effusion).

The patients were assessed for their remission status according to the Task Force on Remission Definitions in SLE based on the absence of clinical disease activity, as measured using a clinical SLE Disease Activity Index—2K=0 and a physician global assessment<0.5. The patients used antimalarials, low-dose glucocorticoids and/or immunosuppressive therapies, and the treatment used was recorded.[1] The Schirmer test was used as an objective indicator of dry eyes in the patients (<5 mm/5 min in both eyes). Serositis findings (pleural effusion and pericardial effusion) were obtained using echocardiography and CT imaging methods. The anticardiolipin antibody (aCL) IGM-IGG and anti-beta2 glycoprotein I antibody (anti-beta2GPI) IGM-IGG levels were assessed using an ELISA test. Lupus anticoagulant tests are in vitro coagulation tests that rely on the phospholipids in the test.

The laboratory parameters assessed were as follows: C reactive protein (CRP) (5–10 mg/dL), erythrocyte sedimentation rate (ESR) (5–20 mm/hour), alanine aminotransferase (3–35 IU/L), aspartate aminotransferase (AST) (5–35 IU/L), lactate dehydrogenase (LDH) (135–248 IU/L), serum creatinine (0.8–1.2 mg/dL), proteinuria (1–150 mg/day), creatine kinase (CK) (35–145 U/L), total protein (66–83 g/L), white blood cell count (WBC) (3.500–10.500×10^9/L), platelet count (PLT) (150.000–450.000×10^9/L), neutrophil (NEU) (2–7.5×10^9/L), complement component 3 (C3) (80–180 mg/dL), complement component 4 (C4) (16–48 mg/dL), anti-double-stranded DNA (dsDNA) (positive>20, negative<20 IU/mL), ANA, aCL IGM-IGG (low titer<40 units, moderate-to-high titer≥40 units) and anti-beta2GPI IGM-IGG (low titer<40 units, moderate-to-high titer≥40 units).

Statistical analysis

The statistical analyses were conducted using the Statistical Package for Social Sciences V.28 programme for Windows. Normally distributed variables were expressed

Table 1 Demographic, clinical and laboratory characteristics of the patients

Characteristics	Value
Female, n (%)	16 (51.6)
Age, years, mean (SD)	30.7 (3.8)
Age of disease onset, mean (SD)	27.7 (3.8)
Disease duration at onset of treatment, years, mean (SD)	1.9 (0.7)
Follow-up, years, mean (SD)	3.1 (0.9)
Remission, n (%)	11 (35.4)
Low disease activity, n (%)	14 (45.2)
Flare, n (%)	6 (20.6)
Alive, n (%)	30 (96.8)
Dead, n (%)	1 (3.2)
ANA (>1/80), n (%)	29 (93.5)
ANA (<1/80), n (%)	2 (6.4)
aCL IGM	2 (6.4)
aCL IGG	2 (6.4)
anti-beta2GPI IGM	2 (6.4)
anti-beta2GPI IGG	2 (6.4)
Lupus anticoagulant	1 (3.2)

aCL, anticardiolipin antibody; ANA, anti-nuclear antibody; anti-beta2GPI, anti-beta2 glycoprotein I antibody; IGM, immunoglobulin M; SD, standard deviation.

as the mean± standard deviation (SD), skewed variables as the median interquartile range (IQR) and categorical variables as a number (n) and percentage (%). The clinical and laboratory parameters and treatment-related changes from baseline (before starting intravenous IG therapy) after the end of treatment were calculated using the McNemar test for categorical variables, a paired-samples t-test for parametric variables and the Wilcoxon signed-rank test for non-parametric variables. Statistical significance was determined by accepting p values that were less than 0.05.

RESULTS

31 patients treated with intravenous IG were included in this study. The mean age of the patients was 30.7±3.8 years and 16 (51.6%) of them were women. The number of patients in remission 6 months after the intravenous IG treatment was 11 (35.4%) and the number with low disease activity was 14 (45.2%). The mean follow-up period for the patients was 3.1±0.9, and only one patient died. Other demographic data, the clinical findings and laboratory parameters related to the patients are listed in table 1.

The most common systemic involvement as an indication for intravenous IG was haematological involvement, which was detected in 20 (64.5%) patients. The most common haematological manifestation as an indication for intravenous IG was thrombocytopenia, with eight (25.8%) patients, and the second most common manifestation was pancytopenia, with four (13.8%) patients. The most common adverse event observed during intravenous IG treatment was non-cardiac thoracic angina in four (13.8%) patients, and the other side effects were a fever and headache due to the infusion. Other information regarding the indications for intravenous IG treatment and adverse events is presented in table 2.

Table 2 Indications for intravenous IG therapy and intravenous IG-related adverse events

Indications for intravenous IG	Value
Thrombocytopenia, n (%)	8 (25.8)
Neutropenia, n (%)	3 (9.6)
Pancytopenia, n (%)	5 (16.1)
Haemolytic anaemia, n (%)	4 (12.9)
Myositis, n (%)	2 (6.4)
Pericarditis, n (%)	1 (3.2)
Recurrent infection, n (%)	3 (9.7)
Peripheral neuropathy, n (%)	2 (6.4)
Skin manifestations, n (%)	3 (9.7)
Adverse events	
Non-cardiac thoracic angina, n (%)	4 (12.9)
Infusion-related reaction (fever), n (%)	3 (9.7)
Infusion-related reaction (headache), n (%)	2 (6.4)

IG, immunoglobulin.

When the clinical parameters were evaluated after the intravenous IG treatment compared with baseline, statistically significant changes were found for fatigue, myalgia, arthritis/arthralgia and Raynaud's phenomenon (p<0.001). Following the intravenous IG treatment, skin rashes and oral aphthous ulcers showed a statistically significant improvement as mucocutaneous involvements (p=0.004 and p=0.008, respectively). Pleural effusion and pericardial effusion showed statistically significant changes when serous involvement was assessed following the intravenous IG treatment in comparison to the baseline (p=0.008, p=0.031). The following laboratory markers showed statistically significant changes between the beginning and end of the intravenous IG treatment: WBC, NEU, PLT, CK, LDH, AST, CRP, ESR, total protein, proteinuria anti-dsDNA, C3 and C4 (p<0.001). Changes in the clinical findings and laboratory parameters after the intravenous IG treatment compared with baseline are shown in table 3.

Intravenous IG therapy was usually prescribed for refractory disease despite standard therapy, but some patients were also started on therapy because of a recurrent infection or contraindications to alternative immunosuppressive therapy. The weekly dosage of glucocorticoids administered as a medical treatment following the intravenous IG treatment was shown to change statistically significantly from the baseline (p<0.001). The frequency of cyclophosphamide

Table 3 Baseline characteristics of patients and characteristics after treatment with intravenous IG

	Baseline	After treatment	P value
Clinical involvements			
Fatigue, n (%)	29 (93.5%)	17 (54.8%)	<0.001
Myalgias, n (%)	25 (80.6%)	11 (35.5%)	<0.001
Fever, n (%)	21 (67.7%)	11 (35.5%)	0.002
Oral aphthae, n (%)	24 (77.4%)	16 (51.6%)	0.008
Dry mouth, n (%)	21 (67.7%)	11 (35.5%)	0.002
Dry eyes, n (%)	24 (77.4%)	14 (45.2%)	0.002
Petechiae/purpura, n (%)	14 (45.1%)	5 (16.1%)	0.008
Arthralgia/arthritis, n (%)	24 (77.4%)	13 (41.9%)	<0.001
Raynaud phenomenon, n (%)	18 (58.1%)	9 (29.1%)	<0.001
Skin rash, n (%)	17 (54.8%)	8 (25.8%)	0.004
Pleural effusion, n (%)	14 (45.1%)	6 (19.4%)	0.008
Pericardial effusion, n (%)	11 (37.9%)	6 (19.4%)	0.031
Laboratory parameters			
WBC ($\times 10^9$/L), mean (SD)	4.3 (2.1)	7.3 (1.5)	<0.001
NEU (mm^3), mean (SD)	2.6 (0.8)	5.1 (1.2)	<0.001
PLT ($\times 10^9$/L), mean (SD)	94.5 (65.3)	220.1 (101.2)	<0.001
CK (IU/L), median (IQR)	60 (53)	28 (47)	<0.001
LDH (U/L), median (IQR)	369 (108)	203 (38)	<0.001
ALT (U/L), mean (SD)	84.8 (101.8)	27.6 (21.4)	0.002
AST (U/L), mean (SD)	53 (61)	27.2 (16.2)	<0.001
Creatinine (mg/dL), mean (SD)	1.5 (0.7)	1.1 (0.7)	0.008
CRP (mg/dL), mean (SD)	96.9 (44.5)	20.5 (18.3)	<0.001
Total protein g/L, mean (SD)	65 (8.1)	73 (12.2)	<0.001
ESR (mm/hour), mean (SD)	82.7 (35.9)	41.2 (25.1)	<0.001
Proteinuria (mg/day), mean (SD)	1018.3 (1315.4)	201.4 (169.6)	<0.001
Anti-dsDNA, mean (SD)	64.9 (16.4)	19.1 (10.4)	<0.001
C3, mean (SD)	75.1 (26.9)	109.8 (30.3)	<0.001
C4, mean (SD)	14.7 (14.4)	28.2 (16.3)	<0.001

ALT, alanine aminotransferase; Anti-dsDNA, anti-double stranded DNA; AST, aspartate aminotransferase; C3, complement component 3; C4, complement component 4; CK, creatine kinase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IG, immunoglobulin; LDH, lactate dehydrogenase; NEU, neutrophil; PLT, platelet count; WBC, white blood cell count.

use as a medical treatment after intravenous IG treatment showed a statistically significant change (p=0.016). No statistically significant changes were detected in other immunosuppressive drugs used as

Table 4 Medical treatments used before and after intravenous IG

Treatments	Before intravenous IG	After intravenous IG	P value
Corticosteroid dosage, mg/week, mean (SD)	268.9 (172.6)	47.7 (14.4)	<0.001
Hydroxychloroquine, n (%)	29 (93.5%)	26 (83.9%)	0.083
Methotrexate, n (%)	21 (67.7%)	17 (54.8%)	0.344
Azathioprine, n (%)	24 (77.4%)	19 (61.3%)	0.063
Mycophenolate mofetil, n (%)	23 (74.2%)	19 (61.3%)	0.125
Cyclophosphamide, n (%)	17 (54.8%)	10 (32.3%)	0.016
Rituximab, n (%)	10 (32.3%)	14 (48.2%)	0.125

IG, immunoglobulin; SD, standard deviation.

medical treatment after the intravenous IG treatment (p>0.05) (table 4).

DISCUSSION

In this study, we analysed 31 patients with SLE, mostly due to active steroid-resistant haematological involvement and/or resistance to immunosuppressive therapy, and especially recurrent infections, who were treated with intravenous IG. The treatment resulted in significant improvements in the constitutional symptoms, haematological involvement, joint findings and skin involvement, as well as improvements in the haematological indicators, muscle enzymes and disease activation parameters in the laboratory findings. Furthermore, there was a reduction in the requirement for the dosage of glucocorticoids. The frequency of cyclophosphamide use decreased due to confusion between the indications for intravenous IG and the side effects of cyclophosphamide. The use of intravenous IG in patients with SLE continues to leave treating physicians with many open questions. Some data support the use of intravenous IG in patients with refractory or severe disease, and it is routinely prescribed in patients with SLE. Guidelines for the use of intravenous IG are lacking, and no large cohort studies or large randomised controlled trials support the use of intravenous IG. On the other hand, its high cost is still a major concern limiting its use.

In inflammatory rheumatic diseases, some data support the use of intravenous IG in patients with refractory or severe disease and intravenous IG is routinely prescribed.[8] Intravenous IG has long been used as a rescue drug in patients with SLE.[13] However, the current data on the use of intravenous IG in patients with SLE are based on numerous case reports and some observational studies. We believe that this research will make a significant contribution to the literature.[9]

In a study on 92 patients who received intravenous IG treatment for a diagnosis of antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis, the most common intravenous IG indication was ear, nose and throat involvement, followed by pulmonary involvement.[14] In a study by Tandaipan *et al*[15] on patients with systemic sclerosis, myositis was the most common intravenous IG indication in 78 patients receiving intravenous IG treatment. This was followed by gastrointestinal involvement and cutaneous involvement. In another study, the conditions that caused intravenous IG indications in patients with idiopathic inflammatory myositis were determined to be refractory myositis and neoplasia, respectively, while in terms of organ involvement, the muscles and the oesophagus were reported to be the most commonly affected organs.[16] In a study on 52 patients with SLE, the most common condition causing an intravenous IG indication was skin involvement, followed by haematological involvement.[8] Haematological involvement was shown to be the most common reason for the use of intravenous IG treatment among the 20 patients with SLE in a study by Levy *et al*.[7] In a study that included 63 patients with SLE, intravenous IG treatment was mostly given due to haematological involvement.[17] In our study, the most common involvement that created an indication for intravenous IG use in patients with SLE was haematological involvement, and the second most common was skin involvement.

Remarkably, we identified clinical findings and laboratory parameters that may help predict an SLE patient's response to intravenous IG. Significant improvements were detected in acute-phase values, dsDNA and complement levels, which are predictive factors for intravenous IG treatment.[18] Significant regression was found in the proteinuria and serum creatinine parameters, which indicate renal involvement and are among the prognostic factors associated with an increased mortality in patients with SLE.[19 20] In a study conducted on patients diagnosed with idiopathic inflammatory myositis, an improvement in myalgia and the CK and LDH levels, which are predictive factors for a good response to treatment, was observed with intravenous IG treatment, as well as a significant improvement in the symptoms of patients with skin involvement who responded poorly to treatment.[16]

The prevalence and characteristics of the drug-related adverse events identified in our study are consistent with those reported in other studies and mostly include infusion reactions.[21] In the majority of cases, adverse events were mild and were usually represented by non-cardiac thoracic angina or a fever. Cerebral events have also been reported previously, but were mild in our patients and resolved spontaneously within a few hours.[22]

In the majority of patients, intravenous IG was initiated after initial therapy with glucocorticoids alone or in combination with at least one immunosuppressive drug. In the majority of the patients, it was prescribed immediately after immunosuppressive failure, and in a small number of patients, it was used as the first treatment option. In a study conducted by Barsotti[16] and colleagues on patients with idiopathic inflammatory myopathy, intravenous IG treatment was mostly given after immunosuppressant treatment. A significant decrease in the weekly glucocorticoid dose and cyclophosphamide use was found after the use of intravenous IG in inflammatory rheumatic diseases.[23] Our study was found to be compatible with the literature in terms of immunosuppression and intravenous IG use. Since the majority of our patients were only treated if they were refractory to normal care, and there is a dearth of literature data on intravenous IG usage as a first-line therapy for SLE, we are unable to endorse its use.[24] Nonetheless, our findings might indicate that, in some clinical situations, starting intravenous IG treatment for refractory illness early on is advantageous.

According to the data presented in our article, early treatment initiation may be linked to an improved clinical response, particularly in patients with high disease activity, by identifying positive and negative predictive factors affecting disease exacerbation and response on intravenous IG discontinuation. The main limitations of this study are that

it is retrospective and single-centre. Furthermore, we were unable to verify the onset timing of the favourable response to intravenous IG that has been previously reported due to its retroactive character.

CONCLUSIONS

To the best of our knowledge, this study comprises the largest reported cohort of patients with SLE receiving intravenous IG, allowing for the evaluation of post-treatment laboratory parameters and clinical findings. Not only does our study validate the effectiveness of this treatment in patients with refractory disease or contraindications to standard drugs, but it also offers insights into the clinical and laboratory features of patients who are most likely to respond to the treatment and those who are most likely to relapse after the treatment is stopped. This treatment was also evaluated as safe with a very low rate of side effects, which are mostly mild. Given the high expense of intravenous IG, we think it is critical to determine the parameters that predict a patient's response to this therapy and, consequently, to choose the most suitable candidates for it. These findings need to be confirmed with larger patient populations and prospective studies.

Contributors MNK conceptualised the idea and study design and was the guarantor. MNK, ÖK and MC collected the patients' samples and clinical data. MSÖ and EÇG prepared the samples for laboratory investigations and performed the laboratory analysis. MNK and ÖK performed the acquisition and interpretation. SY, MNK and ÖK worked on the analysis and interpretation of results and drafted the manuscript. All the authors reviewed the results and approved the final version of the manuscript.

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