

Evaluation of Intravenous Immunoglobulin G treatment in Outpatients Rheumatology Practice

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ABSTRACT

Objective: Intravenous immunoglobulin is an alternative therapeutic agent that can be used off-label in many autoimmune rheumatological diseases. The aim of this study is to evaluate the autoimmune rheumatological diseases characteristics in which intravenous immunoglobulin therapy is used and the efficacy and safety of this therapy.

Methods and Methods: We performed a retrospective review of 133 patients with autoimmune rheumatological disease who received at least 1 course of intravenous immunoglobulin treatment at Hacettepe University Rheumatology Outpatient Clinic between January 2013 and December 2020. The autoimmune rheumatological disease demographic and clinical features, organ involvements, treatment phases (primary-secondary or infection), treatment responses and adverse effects were evaluated.

Results: A total of 79% (n=105) patients were female and the mean±SD age was 45.5±16.9 years. The most common underlying rheumatic diseases were systemic lupus erythematosus (35%, n=47) and dermatomyositis/polymyositis (35%, n=47). Intravenous immunoglobulin therapy was most commonly used for resistant/relapsed myositis and haematological involvement. The median (IQR) intravenous immunoglobulin treatment course was 6.5 (13) and the duration of intravenous immunoglobulin treatment was 10.8 (24) months. Although it is used as second-line therapy in 77% of patients, complete clinical response was observed in 32% and partial response in 47%. There was a significant reduction in the median (IQR) steroid doses (methylprednisolone or equivalent dose) patients received from baseline after intravenous immunoglobulin treatment [30 (33) vs 8 (12), p<0.0001]. It was observed that the use of conventional disease-modifying antirheumatic drugs decreased after intravenous immunoglobulin treatment and the use of rituximab increased. Adverse effects associated with intravenous immunoglobulin treatment (10%) and discontinuation (4%) were found to be very low.

Conclusion: Intravenous immunoglobulin treatment was commonly given in systemic lupus erythematosus and dermatomyositis/polymyositis patients because of hematological involvement and resistant/relapsed myositis in our study, respectively. Although it is mainly the second-line treatment, two-thirds of the patients achieved a complete/partial response. Side effects and related discontinuation due to intravenous immunoglobulin treatment are very few.

Keywords: Autoimmune rheumatological diseases, intravenous Immunoglobulins, treatment

INTRODUCTION

Intravenous immunoglobulin (IVIg) is a blood product containing the pooled polyclonal immunoglobulin (Ig) of thousands of healthy donors. The mechanisms of action of IVIg are complex. These include Fc- and Fab-mediated mechanisms, complement activation, neutralization of anti-idiotypic antibodies, and modulation of various inflammatory mediators, such as immune cells and cytokines. In some cases, the specific mechanisms of these autoimmune processes are still not elucidated [1]. IVIg has a featured role as an immunomodulatory and anti-inflammatory agent, mostly used "off-label", in autoimmune rheumatic diseases (ARD), except immunodeficiency and dermatomyositis [2, 3]. In some small studies have shown the efficacy of IVIg in diverse ARD such as dermatomyositis/polymyositis (DM/PM), systemic lupus erythematosus (SLE) and antineutrophil cytoplasmic antibody-associated vasculitis (AAV) [2, 4-6]. IVIg is generally considered a safe therapy, and most of the side effects are mild and may be ameliorated with slower rates of infusion, premedication, and hydration [7-9].

Still, IVIg is often administered when conventional therapy fails or no alternative therapy exists, and mixed outcomes have been demonstrated across a wide range of diseases in which the etiology remains elusive. The applications of IVIg have expanded in both adult and pediatric diseases [10].

The aim of this study was to determine the clinical features of ARD patients who require IVIg treatment, the efficacy and safety of the IVIg treatments in a tertiary hospital.

MATERIALS and METHODS

Patients who received IVIg therapy between January 2013 and December 2020 at the Hacettepe University Hospital Rheumatology outpatients clinic (which is a tertiary hospital), were retrospectively identified from the medical records. Patients who used IVIg treatments as replacement therapy of primary immunodeficiency were excluded from the study. Additionally, 12 patients were excluded due to insufficient information. Therefore, a total of 133 patients with complete data available were included in this study.

The following information was recorded for each patient: demographic features, the patients' diagnoses, clinical features of ARD, IVIg dosage, number of IVIg treatment days, organ involvements requiring IVIg treatment, disease activity, treatment stage as primary, secondary or due to infection, IVIg treatment responses, relapses and IVIg-related adverse effects. Disease-modifying antirheumatic agents (DMARD) and biological treatments used by the patients before, during and after IVIg treatment were recorded. Post-treatment response assessments were categorized as complete response, partial response, and no response, according to expert physician opinion, using physical examination, acute phase reactants, and serological markers. Of the 9 patients had insufficient data to evaluate the treatment responses. Glucocorticoid doses were recorded as methylprednisolone and its equivalent.

It was determined that all of the patients who underwent IVIg therapy were provided antipyretics and antihistamines in order to reduce the side effects. In order to determine the IVIg-related side effects, we searched the file records.

The protocol for this study was approved by the Hacettepe University Hospital Ethics Committee (KA-21072).

The statistical data was calculated using the Statistical Package for Social Sciences (SPSS) version 24.0 for Windows (SPSS Inc, Chicago, IL, USA). A descriptive statistical analysis was conducted, and because the age at diagnosis was not normally distributed, the data was expressed as the median and interquartile range. The qualitative data was expressed as number and percentage. The Chi-squared test was used to compare the qualitative data, and the Pearson correlation test was used for the correlation analysis. A $p < 0.05$ was considered significant.

RESULTS

A total of 133 patients ($n=105$, 79% female) were included in this study. The mean \pm SD age was 45.5 ± 16.9 years. The median (IQR) IVIg treatment courses was 6.5 (13) and the duration was 10.8 (24) months. Routes of administration of IVIg therapy,

Table 1. Rheumatological diseases characteristics, clinical features and response assessment of intravenous immunoglobulin treatment

Rheumatological diseases features	n (%)
Underlying rheumatic disease	
- Systemic lupus erythematosus	47 (35)
- Dermatomyositis/Polymyositis	47 (35)
- ANCA-associated vasculitis	7 (5)
- Others	32 (25)
Clinical features and response assessment of IVIg treatment	
IVIg administration method	
- 2 gr/5 days	82 (62)
- 2 gr/2 days	3 (2)
- 0.4 gr/1 day	22 (17)
- Others	26 (20)
IVIg indications	
- First-line	18 (14)
- Second-line	103 (77)
- Infection	5 (4)
- Unknown	7 (5)
Treatment response	
- Complete response	42 (32)
- Partial response	62 (47)
- No response	20 (15)
- No assessment	9 (6)
Adverse effects due to IVIg treatment	14 (10)
Discontinuation of IVIg treatment due to adverse effects	5 (4)
Relapse	43 (32)
- IVIg re-treatment after relapse, n (%)	22 (51)

IVIg; Intravenous immunoglobulin

clinical and follow-up features are shown in Table 1. Most of the patients (62%) received IVIg treatment from 2 g/kg to 5 consecutive days.

When the indications for the IVIg administration were examined, the most common underlying ARDs were SLE (35%, n=47) and DM/PM (35%, n=47) (Table 1). All of the reasons for IVIg administration were shown in Figure 1. In the evaluation of disease-specific IVIg administrations; the most common causes in SLE patients were as follows; resistant/relapsing hematologic (55%), renal (16%), neurologic (11%) and cutaneous (11%) involvements or during pregnancy for active disease (5%). In DM/PM patients, the most common cause was resistant skeletal muscle involvement (76%), and cutaneous (15%) involvement. In AAVs the most common causes were peripheral neuropathy (71%) and pulmonary hemorrhage (29%). In SLE patients. IVIg was used as second-line therapy in 77% of patients, %14 as a first-line therapy and %4 for an

infectious disease. The IVIg treatment responses were as follows: complete clinical response in %32, partial clinical response in 47% and unresponsive to IVIg in 15%. Evaluation of treatment responses according to IVIg administration phases was shown in Table 2. At the follow-up of patients relapse was seen in 32% and 51% of those patients needed IVIg retreatment. There was no difference in relapse rates among ARDs receiving IVIg treatment ($p=0.118$) and whether the reason for administration was first-line or second-line therapy.

Adverse effects were observed in 10% of patients and IVIg treatment was discontinued in 4%. The frequency of any adverse effects was similar in the groups according to IVIg doses ($p=0.678$), IVIg administration lines (0.164), and ARD patient groups (0.601).

Of the 89% patients were taking glucocorticoids concurrently with IVIg treatment. In comparisons

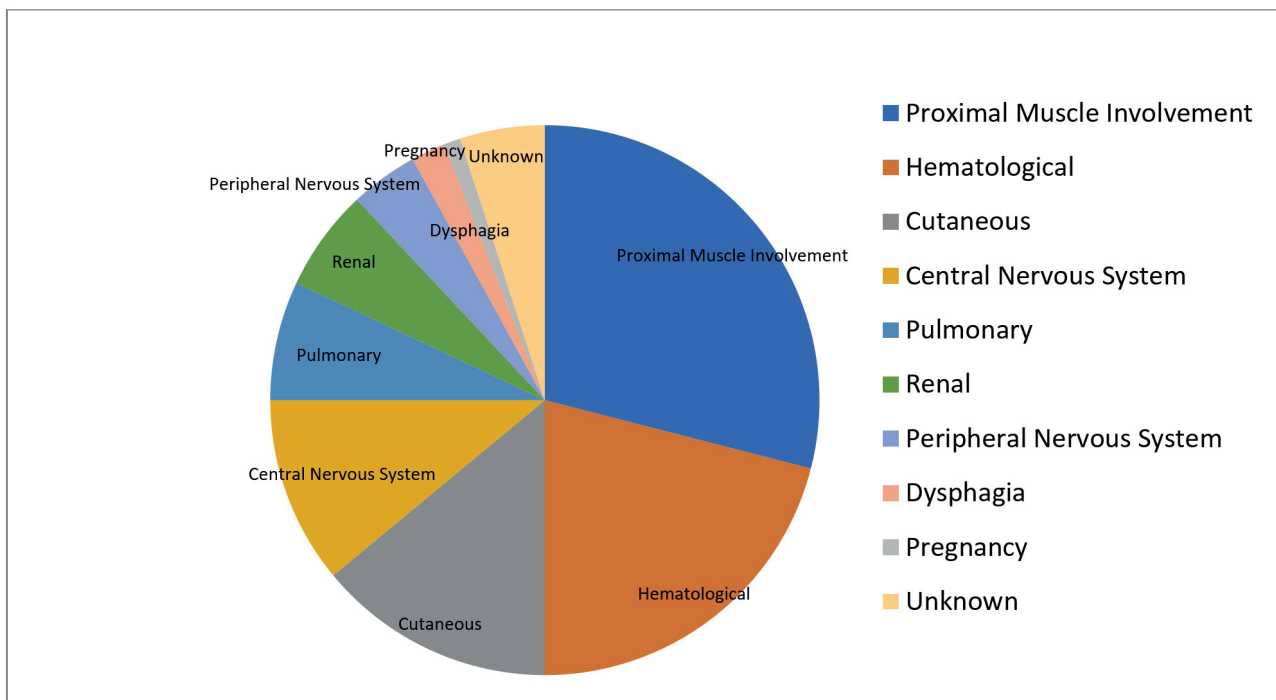


Figure 1. Requiring intravenous immunoglobulin G according to organ involvement

Table 2. Evaluation of treatment responses according to intravenous immunoglobulin administration phases

	First-line, n=18 (%)	Second-line, n=101 (%)	p
Complete response	11 (61)	31 (31)	0.019
Partial response	7 (39)	52 (51)	
No response	0	18 (18)	

of the patients receiving IVIg with glucocorticoid, the frequency of adverse events ($p=0.850$), IVIg treatment discontinuation ($p=0.150$) and relapse ($p=0.750$) were similar to those patients not. After IVIg treatment, the baseline median (IQR) glucocorticoid doses were reduced statistically significantly [30 mg/day (33) to 8 mg/day (12), $p<0.0001$], and the frequency of conventional immunosuppressive was reduced and the frequency of rituximab was increased (Figure 2).

DISCUSSION

In our cohort, IVIg treatment was commonly used in SLE and DM/PM diseases due to hematological involvement and resistant/relapsed myositis, respectively. Although it was mostly second line treatment, two-thirds of the patients reached a complete/partial response. The frequency of any adverse events and adverse event-related discontinuation due to IVIg treatment were very low.

IVIg treatment in adult rheumatology practice is commonly off-label used to treat several diseases for its immunoregulatory effects, except dermatomyositis. IVIg efficacy could be shown in DM/PM which is refractory to glucocorticoids and DMARDs in small studies, but recently IVIg efficacy for DM was shown in a recent randomized controlled trial (RCT) [2, 11, 12]. Another recent RCT which included 26 Japanese patients, similar muscle test score improvements were found between IVIg and control groups. However, the limitation of this study was that the transition between treatment arms was short to demonstrate IVIg efficacy [13]. The use of IVIg by the European Federation of Neurological Societies and European Dermatology Forum recommends IVIg as second-line in resistant DM/PM or as first-line in severe [14, 15].

In SLE, IVIg treatment may have higher priority in some specific organ/system involvements compared to DM/PM. Autoimmune hemolytic anemia, immune cytopenia, congenital heart block, and neuropsychiatric involvement associated with

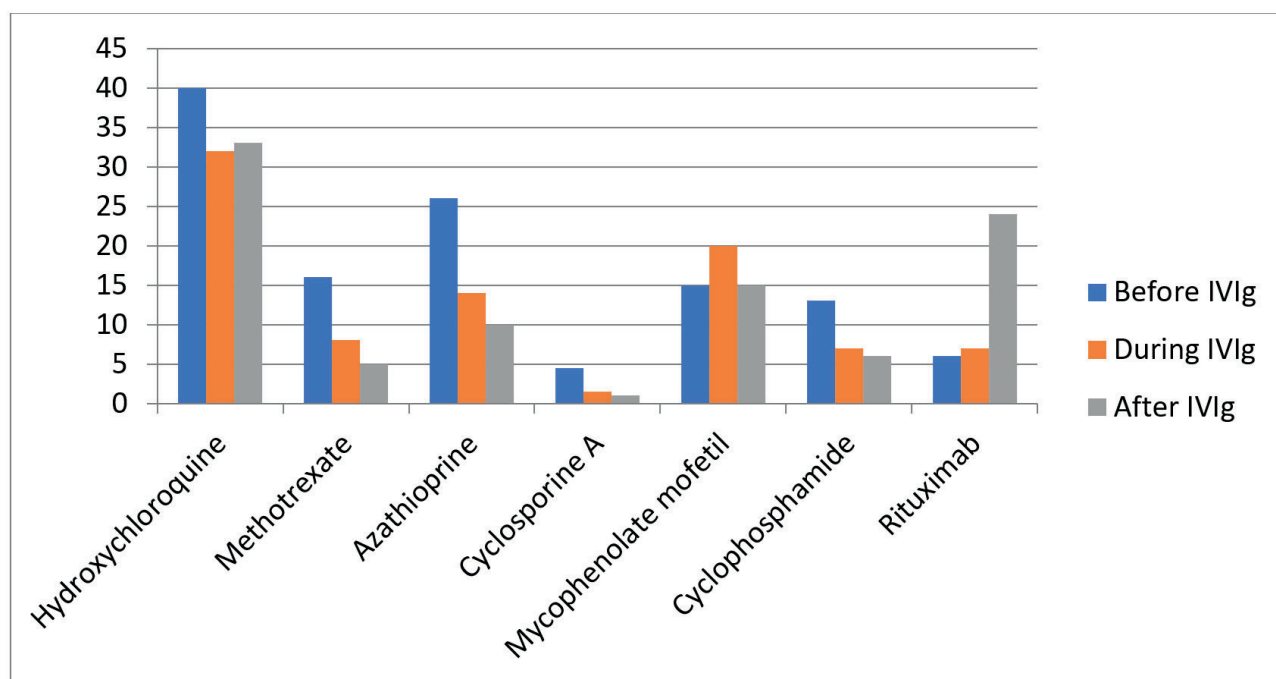


Figure 2. Comparison of immunosuppressive treatments that patients received before, during and after intravenous immunoglobulin G (IVIg) treatment

SLE are the conditions most commonly requiring IVIg therapy [16-19]. In a study which IVIg treatment compared with cyclophosphamide in patients with SLE nephritis, there was no significant difference found in terms of maintaining remission after 18 months follow-up. So, it was thought, IVIg could be an alternative treatment of cyclophosphamide [20]. A study in pregnant SLE patients compared IVIg treatment with steroids and non-steroidal anti-inflammatory drugs (NSAIDs). SLE disease activation was significantly reduced in patients receiving IVIg therapy [21]. Previous studies have also shown that IVIg therapy could be as effective as plasmapheresis in SLE [16, 22]. So, IVIg treatment is useful and effective for both specific involvement and general disease activity for SLE. A combination of glucocorticoids and cyclophosphamide or rituximab treatments has been used for induction of all AAVs. Infact, these therapies have achieved high remission induction rates but some patients may not respond to this therapy. Moreover, some clinical studies demonstrated that IVIg treatment reduced disease activity of AAV and provided more treatment response [5, 23, 24]. In our study, IVIg treatment was given most frequently in DM/PM and SLE disease. IVIg use is common in hematological involvements for SLE, myositis for DM/PM and neuropathy for AAV. When all ARDs are considered together, the most common organ involvement for which IVIg were used were resistant/relapsing

myositis in our cohort. In line with the literature IVIg was used as second-line therapy in 77%.

In addition to refractory or life threatening diseases, presence of the infection and pregnancy IVIg treatment is preferred. Infections can both mimic rheumatological diseases and easily accompany the initial findings due to impaired autoimmunity. Although the immune regulatory mechanism had main roles in ARD including Fc-mediated inactivation of macrophages, consumption of activated complement proteins, neutralization of pathogenic autoantibodies by idiotype antibodies, and correction of cytokine imbalance, the supplementation of IVIg seems to be significant for immunocompromised hosts, and may be a life-saving treatment option when the presence of infection and underlying disease diagnosis is not clear [25, 26]. IVIg preparations may be used without off-label approval is sepsis in our country. We evaluated the ARD patients who required IVIg therapy for underlying disease or infection. So, the proportion of ARD patients who received IVIg treatment due to concomitant infection was 4% in our study. Only 2 patients, both had SLE, were requiring IVIg treatment in our study.

Although there are no RCTs, it was shown in some studies IVIg also markedly reduces the dose of glucocorticoid without clinical or biochemical flare [27, 28]. So, it could be particularly helpful in

patients at risk for glucocorticoid adverse effects. The glucocorticoid dose in our study was reduced from 30 mg/day to 8 mg/day after IVIg treatment.

Given its high cost and the emergence of new effective maintenance treatment, in particular rituximab, prolonged IVIg therapy should probably be avoided in clinical practice [29]. Our findings also showed that the use of DMARD treatments decreased and rituximab treatment increased after IVIg treatment.

Although literature data about IVIg dose protocols for ARDs is limited, the most common treatment regimes are the 2 g/kg in total over either 2 or 5 consecutive days [30]. The optimum duration of IVIg treatment is also unknown. In some studies, clinical improvement and maybe remission was achieved within the first 3 months, so it is thought that IVIg could be discontinued after 3 months in the absence of any clinical improvement [31, 32]. In our study, most of the patients had received IVIg as 2 g/kg for 5 consecutive days. When we compared the rheumatic disease groups according to the IVIg treatment regimen (2 g/kg for 5 days or not), there was no difference among the groups in terms of IVIg treatment regimens ($p=0.616$). Similarly, there was no significant difference among IVIg treatment regimen groups and treatment responses ($p=0.328$). Another vague matter with IVIg treatment is how long the treatment will last. We have been considering that, especially in patients who benefit from the treatment, whether the underlying clinical condition can be treated with other therapeutic options, should be considered on each patient basis.

The frequency of IVIg-related adverse effects varies among studies and were found between 3-33% of the cases, with the most common side effects being fever and rash [31, 33, 34]. The premedication protocols before therapy, the infusions rate, follow-up for delayed onset adverse effects could be responsible for this heterogeneous results

[7, 8]. In our study, any adverse effects occurred in 10% patients and adverse effects leading to discontinuation of IVIg in 4%. Overall, our study demonstrates a good safety profile of IVIg in ARD patients.

Our study had several limitations. This is a retrospective study with data from a single center. Most patients received other medications in addition to IVIg and so an efficacy comparison could not be performed with patients who did not receive IVIg therapy. The duration of treatment responses and relapses were not categorized within a certain period. Reasons for IVIg administration were just separated by organ involvement, and more specific reasons for administration (eg, hemophagocytic syndrome, leukopenia) were not specified. Lastly the disease activities were not evaluated on objective scales and decided by expert opinion.

In conclusion IVIg treatment was given most frequently in DM/PM and SLE diseases due to resistant/relapsed myositis and hematological involvement. The IVIg treatment is not a first-line therapy in rheumatology practice, but it might be useful in some situations such as hematological involvements for SLE, myositis for DM/PM and neuropathy or AAV in our study. When all ARDs are considered together, the most common organ involvement for which IVIg were used were myositis in our cohort. Although it was mostly second line treatment, two-thirds of the patients reached a complete/partial response. The frequency of any adverse effects and adverse effect-related discontinuation due to IVIg treatment were very low.

CONFLICT of INTEREST STATEMENT

We declare that there is no conflict of interest of all authors in this work. No financial support was provided for the conduct, preparation, collection, analysis, interpretation and writing of the report.

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