Treatment with intravenous immunoglobulins in systemic lupus erythematosus: a series of 52 patients from a single centre

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Abstract

Methods

Some studies have shown the efficacy of intravenous immunoglobulin (IVIG) in the treatment of systemic lupus erythematosus (SLE) but its use still lacks confirmation in large cohorts.

This observational, retrospective, single-centre clinical study included 52 SLE patients who received at least one cycle of IVIG (400 mg/kg/day for 5 days) from January 2001 to February 2011. Twenty-seven SLE patients were treated with IVIG for active disease and concomitant infection, while 26 received the IVIG as resistant to standard therapy. The indications for IVIG in the SLE patients were mainly cutaneous, haematological, neuropsychiatric and heart involvements.

Results

In patients with active disease and concomitant infections, the response to IVIG treatment was a complete remission (n=9), partial remission (n=8), and no response (n=8). We recorded any response (total or partial) in 17 out of 27 patients (62.96%).

In patients with active disease refractory to standard therapy, the response to IVIG treatment was a complete remission (n=6), partial remission (n=12), and no response (n=8). We recorded any response (total or partial) in 18 out of 26 patients (69.23%). Seven of these patients relapsed after a mean time of 8.9 months (3–23 months).

Conclusion

In a long-term study, in the largest published cohort of SLE patients, IVIG was found to be effective in selected manifestations such as haematological and cardiac involvement or when other therapeutic approaches are not available, such as in patients with active disease and concomitant infection.

Key words

intravenous immunoglobulin, IVIG, systemic lupus erythematosus, infections

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Introduction

Intravenous immunoglobulin (IVIG) is a biological agent composed of polyclonal antibodies, derived from the plasma of a large pool of healthy donors. It has been primarily used to treat hypogammaglobulinaemia but has also shown promise in treating autoimmune diseases, inflammatory diseases, and cancer (1-4). The Food and Drug Adminstration (FDA), and the European Medicines Agency (EMA) have approved the use of IVIG for the treatment for some conditions, such as idiopathic thrombocytopenic purpura (ITP), Guillain-Barré Syndrome, and Kawasaki's vasculitis.

However, several studies (4) have shown efficacy of IVIG in the treatment of some clinical and laboratory manifestations of systemic lupus erythematosus (SLE).

SLE is the prototypic multisystem autoimmune disease involving virtually every organ in the setting of major autoantibody production. Based on the severity of disease, add-on therapy has to be warranted. The main therapies used are steroids, immunosuppressant drugs, and hydroxychloroquine. The off-label use of IVIG is centreed on treating patients with either life-threatening situations, concomitant infections or involvement refractory/intolerant to standard therapy (corticosteroids plus immunosuppressive agents).

Available data on the use of IVIG agents in SLE did not rely on randomised controlled trials (RCTs) but on observational studies and case reports (4-7).

IVIG has been used to treat the following manifestations in lupus patients: haemolytic anaemia, thrombocytopenia, pancytopenia, pneumonitis, pleural effusion, pericarditis, myocarditis, nephritis, neuropsychiatric lupus, psychosis, peripheral neuropathy, polyradiculoneuropathy, hypogammaglobulinaemia, and vasculitis (8-11). The most extensive experience is in lupus nephritis (12, 13). There is a single randomised controlled trial of low dose IVIG which reported favourable response as a maintenance therapy in proliferative lupus nephritis (14).

Diverse mechanisms of IVIG may play a role, some synergistically, in the modulation of autoimmune diseases by IVIG. The proposed pathways of IVIG activity encompass interaction with the anti-idiotypic network, interference with the complement and cytokine network, cytolysis of target cells through complement or antibody-dependent cell-mediated cytotoxicity (ADCC), induction of apoptosis of target cells via Fc receptors, the role of Fc receptors - sialic acid at the glycan linked to asparagine of the constant Fc chain of IgG, blockade of co-stimulatory molecules, neutralisation of pathogenic antibodies, and modulation of the activation of costimulatory molecules affecting differentiation of T cells, B cells, and dendritic cells (3). IVIG suppresses the expansion of auto-reactive B lymphocytes through signaling of the FcgRIIB, idiotype-mediated inhibition of B-cell receptors, and neutralisation of cytokines such as the B-cell survival factors B-cell activation factor (BAFF and APRIL) (15).

Furthermore, other mechanisms of IVIG in modulating the immune system have been recently proposed, including 1) the presence of IVIG natural antibodies (exclusively of IgG subclass), involved in the homeostasis of the immune system (16); 2) modulation of IL-17 production by human Th17 cells (17); 3) expansion and stimulation of Treg cells throught newly dentified Treg epitope peptides, called Tregitopes (18).

Thus, in addition to its role in protection against pathogens in primary and secondary immunodeficiency patients, IVIg exerts a number of immunoregulatory functions through its interaction with innate and adaptive immune system and thereby imposing immune homeostasis.

We aimed to report a single-centre clinical study evaluating the beneficial effects of IVIG in the following clinical settings:

1. SLE patients with concomitant infection and active disease;
2. SLE patients refractory or resistant to standard therapy.

Methods

This observational, retrospective, single-centre clincal study included 52 SLE patients attending the Louise Coote Lupus Unit at St Thomas Hospital, London from January 2001 to February

2011 who received at least one cycle of IVIG (400 mg/kg/day for 5 days).

All the patients fulfilled the current ACR classification criteria (19) for SLE. Thirteen patients of the original cohort of 65 patients were excluded as follow: patients not fulfilling SLE ACR Classification Criteria (5 patients); administration of IVIG due to the concomitant diagnosis of common variable immunodeficiency (3 patients); clinical data incomplete (5 patients).

We analysed patients receiving IVIG according to the following indications 1) SLE patients with concomitant infection and active disease 2) SLE patients refractory or resistant to standard therapy.

Patients with active SLE were sub-classified into having moderate flare or severe flare. Severe flares were defined by the involvement of one or more internal organ. All the other clinical manifestations of active disease were recorded as moderate flare.

The outcome was classified as *no response* (0), *partial remission* (1) or *complete remission* (2) according to the global physician assessment (GPA).

The diagnosis of infection was based on the positive culture results of pathogenic microorganism. For those with negative results of microorganism culture, infection was diagnosed by typical symptoms, signs, radiological examination and laboratory evaluations, combined with positive response to the standard antibacterial therapy.

Statistics

Descriptive statistics included means [± standard deviation (SD)] or median (min-max) as appropriate for continuous variables and frequency (percentage) for categorical variables. Rate of initial response to IVIG was compared according to the characteristics of patients using Fisher exact tests for qualitative variables and Mann-Whitney tests for continuous variables. Relapse-free survival rates were estimated according to the Kaplan-Meier method.

Due to the small number of events, multivariate analyses were not performed.

For all analyses, α risk was set at 5%. All analyses were performed using SPSS (version 19.0, IBM, Chicago, IL)

Results

Patient characteristics

Data from 52 patients (45 female and 7 male) were enrolled in our analysis. Demographic, clinical and laboratory characteristics are summarised in Table I. The mean age at the time of first administration was 33.2 years ±9.3. The number of received cycles for each patient ranged from 1 to 16 (mean 1.6 cycles/patient ±2.8), which resulted in a total of 82 cycles of IVIG. Ten patients had secondary APS. Two (n. 5 and 16) of the patients were pregnant at the time of the administration and 2 (n. 33 and 36) were given the infusions in early postpartum period.

Twenty-seven SLE patients were treated with IVIG for active disease and concomitant infection, while 26 received the IVIG as refractory or resistant to standard therapy.

The indications for therapy in the SLE patients are showed in Table I. In brief, they were cutaneous involvement (n=16), haematological involvement (n=13), neuropsychiatric involvement (n=6), heart involvement (n=6), peripheral neuropathy (n=5), joint involvement (n=2), lung involvement (n=1), renal flare (n=1), other manifestations (n=2).

Overall clinical outcome

Table I showed the outcome for each patient, taking into account the infection status.

In patients with active disease and concomitant infections, the response to IVIG treatment was a complete remission (n=9), partial remission (n=8), and no response (n=8). We recorded any response (total or partial) in 17 out of 27 patients (62.96%). Two of these patients (n. 22, 46) relapsed (Fig. 1) after a mean time of 120 and 2 months respectively. Infections included sepsis (n=12), pneumonia (n=8), urinary tract (n=4), and skin (n=2)

In patients with active disease refractory to standard therapy, the response to IVIG treatment was a complete remission (n=6), partial remission (n=12), and no response (n=8). We recorded any response (total or partial) in 18 out of 26 patients (69.23%). Seven of these patients relapsed (Fig. 1) after a mean time of 8.9 months (3–23 months). Five out of 26 (19.23%) patients had a severe flare and only 2 of those did not respond to IVIG treatment

Previous therapies before IVIG are shown in Table I.

No statistically difference was observed stratifying patients for the infection status in term of rate of recurrences. Nevertheless, patients with concomitant infection at the time of IVIG administration who experienced any benefit (complete remission or partial remission) had a longer time free from relapse compared to those without infection (57.07±45.13 and 48.41±41.42, respectively, p=0.002, Fig. 1).

Side effects

Following the first treatment course, only a minority of the patients experienced adverse events (AE). Mild AE's included headache (n=8), and cutaneous rash (n=3).

Two patients experienced severe AE (n. 48, 49). The first one had digital infarct leading to amputation, and the second had a fatal acute coronary thrombosis.

Clinical outcome according to main clinical manifestation

– Skin

The skin involvement was the main indication in our cohort (16/52 patients; 38/82 cycles). Seven patients had subacute cutaneous lupus, 5 patients had discoid lupus, 3 patients had cutaneous vasculitis and 1 patient had acute cutaneous lupus (bullous). Four of them had concomitant infection. The response to IVIG treatment was a complete remission (n=1), partial remission (n=9), and no response (n=6). Nine of the 10 patients who experienced any benefits from IVIG treatment had relapses (mean time free from flare 45±44.5 months). In these patients, the decision was to repeat the IVIG infusion, which explains why these patients had more than 1 cycle of IVIG (1 to 16 cycles/patient), with an average of 2.4 cycles/patient.

– Haematological

Cytopenias were the second most prevalent indication (13 patients; 18/82 cycles). The diagnoses were neutropenia (1 patient), haemolytic anaemia

Table I. Demographic, clinical and laboratory characteristics of 52 SLE patients treated with IVIG.

Pt	Age	Sex	Diagnosis	No. cycles	Severe Flare	Infection	Flare Type	Outcome	Previous therapy
1	41	F	SLE	1	N	N	Thrombocytopenia	No response	Steroids Pulses
2	31	F	SLE+APS	1	N	Y	Miositis	Partial remission	CYC, MTX
3	41	F	SLE	3	N	N	SCLE	Partial remission	MMF
4	38	F	SLE	1	N	Y	Neutropenia	Total remission	–
5	30	F	SLE	1	Y	Y	Pericarditis	Total remission	MMF
6	46	F	SLE	6	N	Y	Pancytopenia	Partial remission	AZA, Splencectomy, CsA, RTX, CYC
7	36	F	SLE	1	Y	Y	Miocarditis	Total remission	–
8	23	F	SLE	1	Y	Y	NPSLE	Partial remission	AZA, MTX,
9	56	F	SLE	1	N	N	Peripheral Neuropathy	Total remission	CYC, AZA, MTX, MMF, CSA, Infliximab, Etanercept
10	35	F	SLE	1	N	N	SCLE	Partial remission	AZA, MTX, HCQ, 6MP, CSA, Imflizimav, I.M. Gold
11	22	M	SLE+APS	1	N	Y	Discoid Lupus	Partial remission	AZA
12	51	F	SLE+APS	1	N	Y	Thrombocytopenia	No response	–
13	34	F	SLE+APS	1	Y	Y	Miocarditis	Total remission	–
14	47	F	SLE	1	N	N	Peripheral Neuropathy	Partial remission	AZA, MTX, MMF
15	44	M	SLE	1	N	Y	Discoid Lupus	No response	AZA, MTX, TLD, DPS,HCQ
16	32	F	SLE	1	Y	Y	Pericarditis	Total remission	–
17	31	M	SLE	16	N	N	Discoid Lupus	Partial remission	AZA, MTX, MMF, TLD, MPC, HCQ
18	43	F	SLE	1	N	N	SCLE	No response	AZA, MTX,MPC, HCQ
19	30	F	SLE+APS	1	N	Y	Thrombocytopenia	Total remission	HCQ
20	43	F	SLE	1	N	N	SCLE	Partial remission	AZA, MTX, MMF, MPC, HCQ
21	28	F	SLE+APS	1	Y	Y	Peripheral Neuropathy	Partial remission	MMF
22	36	F	SLE	2	N	Y	SCLE	Partial remission	AZA,MMF, HCQ, MPC, THD
23	46	M	SLE	1	N	N	Discoid Lupus	Total remission	–
24	23	F	SLE	1	N	Y	Haemolytic Anaemia	Total remission	–
25	41	F	SLE	1	N	N	SCLE	Partial remission	STEROIDS PULSES
26	49	F	SLE	1	Y	Y	Ischaemic Bowel Involvement	No response	MTX
27	44	F	SLE	1	N	N	Cutaneous Vasculitis	No response	–
28	34	F	SLE	1	N	N	SCLE	No response	AZA, MMF,TLD
29	17	F	SLE	1	N	Y	Pancreatitis	Total remission	–
30	24	F	SLE	1	N	N	Pancytopenia	Partial remission	CYC, RTX, Plasmapheresis, Steroids Pulses
31	23	F	SLE+APS	1	Y	N	NPSLE (Psycosis)	Partial remission	Steroids Pulses
32	18	F	SLE	1	N	N	Thrombocytopenia	Total remission	MMF, HCQ
33	27	F	SLE+APS	1	N	N	Haemolytic anaemia	Partial remission	–
34	21	M	SLE	1	N	Y	Pancytopenia	Partial remission	CYC, Steroids Pulses
35	43	F	SLE	1	N	N	SCLE	No response	–
36	32	F	SLE	1	N	N	Arthritis	Total remission	–
37	28	F	SLE	1	Y	N	Renal Flare	No response	–
38	37	F	SLE	1	N	N	Peripheral Neuropathy	Total remission	MMF
39	31	F	SLE	2	N	N	Arthralgia	Partial remission	/
40	19	F	SLE	1	Y	N	NPSLE	Total remission	CYC, MPC
41	30	F	SLE	1	N	Y	Thrombocytopenia	Total remission	AZA, MTX
42	35	M	SLE	1	Y	N	Miocarditis	Partial remission	–
43	26	F	SLE	1	Y	Y	NPSLE	No response	–
44	29	F	SLE+APS	1	Y	Y	NPSLE (Peripheral Neuropathy + Psycosis)	Total remission	–
45	21	M	SLE	1	N	Y	Thrombocytopenia	No response	CYC, MMF, HCQ
46	32	F	SLE	1	N	Y	Discoid	Partial remission	CYC
47	33	F	SLE	2	N	Y	Pulmonary	No response	–
48	38	F	SLE	1	Y	Y	Miocarditis	No response	–
49	39	F	SLE+APS	1	N	N	Peripheral Neuropathy	No response	–
50	34	F	SLE	2	Y	N	Cns Vasculitis	No response	–
50	34	F	SLE	1	N	Y	Acle	No response	–
51	21	F	SLE	1	N	Y	Thrombocytopenia	Total remission	AZA, MTX, MPC, TLD, HCQ
52	19	F	SLE	5	N	N	Cutaneous Vasculitis	Partial remission	–

SLE: systemic lupus erythematosus; APS; antiphosholipid syndrome; Y: yes; N: no; SCLE: sub-acute lupus erythematosus; ACLE: acute cutaneous lupus; NPSE: neuropsychiatric systemic lupus erythematosus; CYC: cyclosporine; AZA: azathioprine; MTX: methotrexate; MMF: mychophenolate; CsA: cyclosporine A; HCQ: hydroxicloroquine; 6MP: mercaptopurine; RTX: Rituxiamb; TLD: thalidomide; MPC: mepacrine; CNS: central nervous system.

(2 patients), pancytopenia (3 patients) and thrombocytopenia (7 patients). In patient n. 45, use of IVIG was associated with the use of granulocyte colony stimulating factor (G-CSF). All but 3 patients experienced some improvement after IVIG treatment (total remission, n=6, partial response, n=4). The three patients with no response had thrombocytopenia. Only one of those with thrombocytopenia (n. 6) received more than 1 cycle of IVIG, (6 cycles), showing either just partial improvement (2 cycles) or no response (4 cycles). Of note, this same patient had failed several previous medications – namely steroids, azathioprine, cyclosporine, cyclophosphamide and rituxi-

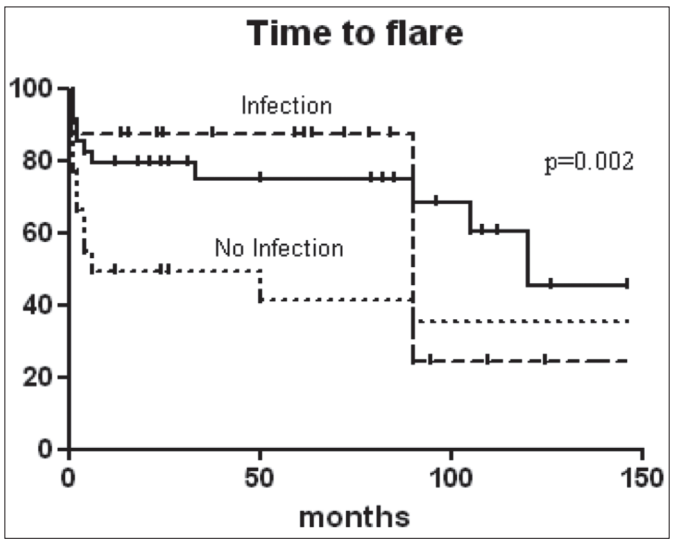

Fig. 1. Time to flare rates estimated according to the Kaplan-Meier method.

mab – and has been already splenectomised. Concomitant infection was present in 9 patients. No statistical difference was observed stratifying patients for the infection status, mainly due to the small number of this sub-cohort.

– Nervous system

Eleven patients had a total of 11 cycles (1 cycle/patient) for nervous system involvement. Five of them had peripheral neuropathy, while 6 were considered to have central nervous system and 1 to have both central and peripheral nervous system involvement. Central nervous system involvement included 2 cases of psychosis, 1 case of CNS vasculitis and 3 of confusional state without any other identified cause.

All the patients but 3 experienced any improvement after IVIG treatment (total remission, n=4, partial response, n=4). In 4 cases, IVIG treatment was indicated for concomitant infection associated with CNS involvement (2 cases) and peripheral neuropathy (2 cases). None of these 4 cases experienced any relapse.

– Cardiac

Six patients had IVIG for cardiac involvement: 2 for pericarditis, 4 for myocarditis. Two of the patients were pregnant (n.5 and 16). Five of them had concomitant infection (n. 5, 7, 13, 16, 48). The response to IVIG treatment was a complete remission (n=4), partial remission (n=1), and no response (n=1). No patient relapsed after IVIG treatment. However, one patient (n. 48) died of myocardial infarction 13 hours after receiving IVIG treatment.

– Musculoskeletal

One patient had IVIG for myositis associated with concomitant infection. Two patients had IVIG for constitutional symptoms associated with arthritis. One of these patients experienced an early postpartum flare (n. 36). All the patients had a good response to treatment. Patient n. 36 relapsed with arthralgia and constitutional symptoms after 12 months.

Discussion

IVIG has long been used as a rescue medication in SLE. However, available data on the use of IVIG in SLE rely on a large number of case reports and some observational studies (4-13), with the exception of a small randomised trial of low dose IVIg in lupus nephritis. As there are no current recommendations/guidelines on the use of IVIG in SLE, many questions remain on when and how to use it.

This observational, retrospective, chart- and database driven, single-centre clinical study aimed to evaluate the beneficial effects and safety profile of high-dose IVIG in the largest series of SLE patients.

The clinical features presented in our cohort at the time of IVIG administration included cutaneous, haematological, neuropsychiatric and cardiac involvement.

Our study emphasises that treatment with IVIG is effective; however the efficacy is not comparable for all the indications.

Skin involvement, refractory to conventional treatment, represented the commonest indication in our cohort. The response to IVIG treatment was a complete remission only in one case and 90% patients who experienced any benefits from IVIG treatment, relapsed in a short period of time. Similar results have been published before in the literature, especially concerning the high relapse rate (20-22). Although the management of skin involvement in SLE can represent a real challenge due to resistance of intolerance to other therapies, IVIG seems not to represent the ideal therapeutic option, especially when other biological treatments are showing promising results in this field (23).

Haematological involvement was the second most prevalent indication. Cytopenias are common in SLE, due either to bone marrow failure, excessive peripheral cell destruction or adverse reactions to medication. Treatment involves steroids, steroid-sparing agents, and splenectomy. Intravenous immunoglobulin has long been also used in SLE cytopenias, with good results reported (24). Our data support this indication, as all the patients but 3 experienced any improvement after IVIG treatment (total remission, n=6, partial response, n=4). Of note, in all but one of these patients the clinical response was recorded after only one cycle of IVIG. The three patients with no response have severe thrombocytopenia unresponsive to previous treatment with high-dose steroids, azathioprine, cyclosporine, cyclophosphamide and rituximab. In all other indications, conclusions are harder to reach, because of the small number of patients in each group. Among the 26 SLE active resistant or intolerant to standard therapy, more than 69% experienced some beneficial effects. It is worthwhile to underline the generally good response to IVIG in patients with cardiac involvement. The response to IVIG treatment was a complete remission in 80% of the cases and these data are in line with those reported in literature (25, 26). However, a note of

caution must be mentioned, as 1 patient died from a fatal myocardial infarction.

In our cohort, more than half of the patients received IVIG because of concomitant infection and 63% of them experienced any response, partial or total remission. We would like to emphasise the advantage of IVIG compared to immunosuppressant drugs or the biologic agents in the management of a challenge situation such as SLE and concomitant infection. Infection is a common problem and has become one of the leading causes of mortality in patients with SLE (27-29).

Amongst the patients with complete or partial response, the time free of flare was 52.1±41.8 (Fig. 1). In this respect, our work is unique because the mean long-term follow-up was very long: 71.56 months (range: 24–156 months).

No statistically difference was observed stratifying patients for the infection status in term of rate of recurrences. However, patients with concomitant infection at the time of IVIG administration who experienced any benefit (complete remission or partial remission) had a longer time free from relapse compared to those without infection (Fig. 1).

IVIG was not used specifically to treat infections or sepsis, as it has not been proven to be effective for these indications (30, 31), but it was considered the safest option to treat SLE activity since immunosuppressive therapies could lead to a worsening of the infection. In these patients, the beneficial effects of IVIG are most probably multifactorial, acting through complement deactivation, receptor blockade, anti-idiotypes, and modulation of cytokine production. Treatment with IVIG was aimed to treat the activity of the disease without producing severe immunosuppression, while the concomitant antibiotic therapy would aim to improve the infection.

This study was not design to investigate the steroid sparing effect of IVIG. However, we observed a reduction in the dose of oral steroid after IVIG treatment (mean prednisone dose before IVIG 12.5±7.5 mg/day *vs*. 7.8±6.7 mg/day after IVIG). According to the ongoing debate (32-34), this observation can support a steroid-sparing role of IVIG in SLE treatment. Further tailored studies are warranted.

We have to report that two patients experienced thromboembolic events (n. 48, 49). Thromboembolic complications in IVIG-treated patients are a result of several factors: hyperviscosity (especially in elderly patients, patients with diabetes mellitus, prior thromboembolic events), hypertension, dyslipidaemia, and high doses of IVIG administered in a rapid infusion rate (12, 29, 35). Both patients who developed thromboembolic events in this study had SLE and antiphospholipid antibodies, one (n. 48) and the other (n. 49) antiphospholipid syndrome and she was anticoagulated because of previous thrombosis. Our rate of thrombosis was lower than reported in other series (7) (2/52 compared to 2/17).

In conclusion, in a long term study in the largest published cohort of SLE patients, IVIG was found to be effective in selected manifestations such as haematological and cardiac involvement or when other therapeutic approaches are not available, such as in patients with active disease and concomitant infection.

We also acknowledge that IVIG use can be limited by its cost; however other approaches including treatments with biological agent can be similarly expensive (36).

IVIG does not seem a effective therapeutic tool for aggressive cutaneous lupus patients, considering the short-term improvement, costs and limited availability of this treatment, especially now that new biologic agents can represent an alternative strategy. Naturally we would recommend that randomized controlled trials are needed to support these observations.

Key messages

- Several studies have shown efficacy of IVIG in the treatment of some manifestations of SLE.
- We found IVIG to be effective in haematological and cardiac involvement in SLE resistant to standard therapy.
- We found IVIG to be effective in patients with active disease and concomitant infection.

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