Intravenous Immunoglobulins in Lupus Nephritis

R.K. Gupta^c M.R.N. Nampoory^c K.V. Johny^a J. Costandi^c I. Francis^b

Departments of ^aMedicine and ^bPathology, Faculty of Medicine, Kuwait University and

^cDepartment of Medicine, Mubarak Al-Kabeer Hospital, Kuwait

Key Words

Systemic lupus erythematosus · Nephritis · Autoimmune hemolytic anemia · Intravenous immunoglobulin

Abstract

Objective: The study is aimed at demonstrating the effectiveness of intravenous immunoglobulin (IVIg) in resistant lupus nephritis. Lupus nephritis was considered resistant when it failed to show adequate clinical and laboratory response to treatment with steroid, azathioprine and pulse cyclophosphamide in combination for a period not less than 1 year. **Methods:** During the past 7 years 4 subjects (M = 1, F = 3) with systemic lupus erythematosus (SLE) and lupus nephritis WHO IV were selected to receive IVIg. Their age ranged from 19 to 48 years. The 3 female patients had severe extrarenal manifestations including skin rash, photosensitivity, fever, headache and severe polyarthralgia requiring large doses of analgesics. The male patient had steroid-dependent, relapsing autoimmune hemolytic anemia (AIHA) in addition to extrarenal manifestations. All subjects had microscopic hematuria, proteinuria (2–6 g/24 h), hypoalbuminemia (24–33 g/l), mild renal impairment (serum creatinine 90–160 µmol/l) and active serology for SLE. These patients had not responded satisfactorily to several courses of steroids, azathioprine and pulses of intravenous cyclophosphamide in 23–180 months. All 4 patients were started and continued on IVIg as per our protocol. **Re-**

sults: During the 9 months to 7.5 years of follow-up, these patients showed excellent response to IVIg. Their extrarenal symptoms had totally disappeared, serological activity subsided, proteinuria decreased (0.5–2 g/24 h), serum albumin improved (30–42 g/l) and renal function remained stable. The subject with AIHA did not suffer any further relapses and his hemoglobin remained above 110 g/l with only 10 mg of prednisolone daily. Repeat renal biopsy done in 2 patients showed definite histological reversal of active lesions. Clinical and immunological improvements might be related to the modulation of macrophage T cell function and enhancement of suppressor T cell function. **Conclusion:** IVIg has shown excellent therapeutic effect as an alternative drug in treatment of renal and extrarenal manifestations of SLE, which are resistant to other modalities of treatment.

Copyright © 2001 S. Karger AG, Basel

Introduction

Systemic lupus erythematosus (SLE) is an immunological disorder for which different therapeutic regimens have already been recommended [1]. Severe cases of SLE are treated with high doses of steroid and cytotoxic drugs, especially if they have proliferative lupus nephritis. While these regimens can be effective, relapses do occur when the treatment periods are short. Moreover this treatment can result in an immunodeficient state and consequent life-threatening infections. Intravenous immunoglobulin

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2001 S. Karger AG, Basel
1011–7571/01/0104–0197\$17.50/0

Accessible online at:
www.karger.com/journals/mpp

Prof. K.V. Johny, MD, FRCP, FACP
Chairman, Department of Medicine
Faculty of Medicine, PO Box 24923
13110 Safat (Kuwait)
Fax +965 5338907, E-Mail kvjohny@hsc.kuniv.edu.kw

Table 1. Clinical data and details of IVIg treatment

Patient No.	Age years	Sex	Treatment prior to IVIg	Duration of SLE prior to IVIg, months	Duration of follow-up on IVIg, months
1	42	F	prednisolone, AZA, cyclophosphamide pulse and PE	180	86
2	43	F	prednisolone, AZA, cyclophosphamide pulse	43	90
3	48	F	chloroquin, NSAID, prednisolone, cyclophosphamide pulses	216	36
4	18	M	prednisolone, AZA, CyA	60	9

AZA = Azathioprine, PE = plasma exchange; NSAID = nonsteroidal anti-inflammatory drugs; CyA = cyclosporine.

(IVIg) is a standard therapeutic agent in different immunodeficiency states [2]. It is used regularly in the treatment of autoimmune diseases such as immune thrombocytopenic purpura, Kawasaki disease, Guillain-Barré syndrome and polymyositis [2, 3]. IVIg is an immunomodulating agent and is capable of modulating SLE in animal models and humans [3]. In addition it can enhance defense against infection. There are various reports on the use of IVIg in SLE. The majority of these studies were in subjects with mainly extrarenal manifestations [4–10]. We herein report our experience with IVIg therapy in 4 patients with resistant SLE and lupus nephritis. This is also the first report of successful treatment of autoimmune hemolytic anemia (AIHA) in IVIg to the best of our knowledge.

Materials and Methods

Subjects

During the past 7 years 4 patients with SLE and lupus nephritis were selected to receive IVIg. Inclusion criteria were: classified as SLE as per ARA criteria [11], presence of severe extrarenal manifestations and severe lupus nephritis [7]. These patients were considered to have resistant lupus nephritis since they did not show adequate clinical and laboratory response to treatment with steroid, azathioprine and pulse cyclophosphamide in combination for a period not less than 1 year. All subjects had treatment with steroid (methylprednisolone pulse, 1 g daily for 3 days followed by oral prednisolone 60 mg daily tapered to 10 mg daily in 6 months). Azathioprine (3 mg/kg/day tapered to 1 mg/kg/day in 6 months), cyclophosphamide pulse (0.5–0.75 g/m² body surface area monthly for 3 months followed by once in 3 months for a total of 2 years only). Subjects with milder forms of renal and extrarenal SLE, advanced renal failure and cerebral lupus requiring plasma exchange were excluded from the study.

All subjects gave informed consent for the treatment. They were evaluated clinically in detail and recorded appropriately. Extrarenal manifestations were recorded in all the patients before and after IVIg therapy using the mean SLAM score, which registers 25 symptoms

and organ manifestations with 7 nonimmunologic laboratory variables [12, 13]. The blood samples for hematological, biochemical and immunological tests were taken at different points of time, just before starting IVIg and thereafter once every 2 months. All subjects had urine microscopic examination and proteinuria measured at similar intervals.

Immunological Examination

Serum complements C3 and C4 were measured by nephelometry. Antinuclear antibodies and anti-DNA antibody were estimated by immunofluorescence antibody technique. ENA, SSA(Ro), SSB(La) and anticardiolipin antibody were measured by ELISA.

Renal biopsies were evaluated by a single pathologist. All renal biopsies were performed under ultrasound localization. Each core of renal tissue was examined fresh under a dissecting microscope and divided into three portions for routine histology, immunofluorescence and electron microscopy. Routine histological examinations were carried out on 5 paraffin sections stained with hematoxylin and eosin, periodic acid Schiff, Gomori's methenamine-silver and trichrome stains. Direct immunofluorescence for deposition of IgG, IgM, IgA, C3 complement and fibrin was performed on cryostat sections. These were then examined under an ultraviolet microscope to detect any immunoglobulin or complement deposition.

Intravenous Immunoglobulins

All patients were treated with IVIg at monthly intervals for 3 months followed by once every 3 months. Each course consisted of 2 g IVIg/kg body weight. The first dose was divided over 5 consecutive days and subsequent doses were given divided over 2 days. We used predominantly Intraglobulin f from Biotest Pharma, Germany. Each dose of IVIg was preceded by chlorpheniramine maleate 4 mg and methylprednisolone 100 mg as a prophylaxis against possible hypersensitivity reaction.

Results

Four subjects with resistant SLE and lupus nephritis underwent IVIg therapy. Table 1 shows demographic features and details of IVIg treatment in these patients. There were 3 females and 1 male with a mean age of 38 ±

Table 2. Outcome of clinical, laboratory and histological parameters

Patient No.	Extrarenal manifestation		Direct SLAM score (n = 25)		Mean serum creatinine $\mu\text{mol/l}$		Mean serum albumin g/l		Mean urinary protein 24 h		Renal histology WHO IV ^a	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
1	headache, body ache joint pain, cutaneous vasculitis	nil	11	3	160	95	28	33	5.3 g	42.3 g	4:2	1:4
2	joint pain, body ache, fatigue, uneasiness	nil	10	2	126	60	30	40	3.5 g	700 mg	4:1	1:4
3	persistent headache, joint pain	nil	8	2	90	75	30	42	1.2 g	210 mg	3:2	not done
4	body ache, joint pain, low-grade fever	nil	10	3	96	65	29	36	1.5 g	620 mg	4:1	not done

Normal values: mean serum creatinine, 60–120 $\mu\text{mol/l}$; mean serum albumin, 35–47 g/l; mean urine protein, <150 mg.

^a Activity:chronicity.

Table 3. Outcome of immunological data

Patient No.	C3/C4		ANA		Anti-DNA	
	pre	post	pre	post	pre	post
1	0.6/0.2	1.1/0.3	1:160	negative	1:40	negative
2	0.5/0.1	0.8/0.3	1:640	1:40	1:10	1:10
3	0.8/0.2	1.1/0.31	1:40	1:10	1:10	1:10
4	0.5/0.1	0.7/0.2	1:2,560	1:160	1:640	1:40

Pre- and post-therapy Acl antibody was negative in all 4 patients.
ANA = Antinuclear antibody.

12 years. The mean duration of SLE prior to IVIg therapy was 120 ± 80 months in these patients. All subjects were on prednisolone, azathioprine and cyclophosphamide pulse treatment regularly prior to starting IVIg treatment. In addition to the above therapy 3 patients had received plasma exchange, chloroquin and cyclosporine, respectively. All subjects continued to have severe extrarenal manifestations prior to initiation of IVIg therapy as shown in table 2. Severe lupus nephritis (WHO IV) with an activity index of 2:4 was found in the renal biopsies of these patients. Proteinuria ranged from 1.2 to 5.2 g/24 h (3.3 ± 1.63 g/24 h) in these patients. All had microscopic hematuria. Hypoalbuminemia ($24\text{--}30$ g/l, 29.3 ± 0.9 g) was present in all subjects with mild renal impairment (serum creatinine 73.8 ± 13 $\mu\text{mol/l}$). All subjects had active lupus serology. The male patient had autoimmune hemolytic anemia (AIHA) and suffered several episodes of

hemolytic crisis requiring large doses of steroid and repeated blood transfusions. Details of clinical, laboratory and histological improvements in these patients are shown in table 3.

During follow-up periods ranging from 9 months to 7 years their extrarenal symptoms resolved. Serological activity decreased except for one parameter (low titers in 3 patients) of antinuclear antibody (table 3, fig. 1). The SLAM score significantly decreased. Proteinuria decreased significantly and serum albumin improved to $30\text{--}40$ g/l after around 15 months from starting IVIg (fig. 2). The renal function remained stable and normal (fig. 3). Repeat renal histology in 2 female patients showed definite histological disappearance of active lesions (fig. 4a, b). The subject with AIHA did not suffer any further relapses and hemoglobin remained above 110 g/l with maintenance therapy of only 10 mg prednisolone daily.

Fig. 1. Competent level before and after starting IVIg treatment. Case 1 = ○; case 2 = △; case 3 = ●; case 4 = ▲.

Fig. 2. Twenty-four-hour urinary protein excretion (—) and serum albumin (---) level before and after starting IVIg treatment. Urinary protein excretion: case 1 = ○; case 2 = △; case 3 = ●; case 4 = ▲. Serum albumin: case 1 = ○; case 2 = △; case 3 = ●; case 4 = ▲.

Fig. 3. Serum creatinine changes before and after starting IVIg treatment. Case 1 = ○; case 2 = △; case 3 = ●; case 4 = ▲.

Fig. 4. Photomicrograph of lupus nephritis taken before and after IVIg treatment in case 1. **a** A glomerulus shows segmental necrotizing changes in capillary tuft. HE. × 200. **b** Following treatment, the glomerulus of the same case above, reveals only a mild degree of mesangial cell proliferation. HE. × 400.

Table 4. Reported case series on IVIg treatment in SLE

Reference	Patients	Responders		Features that were successfully treated with IVIg
		n	%	
Lin et al. [4]	9	3	33	class IV lupus nephritis
Corvetta et al. [5]	3	2	66	encephalitis leukopenia, thrombocytopenia
Maier et al. [6]	7	5	71	thrombocytopenia
Schroeder et al. [7]	11	9	75	arthritis, cytopenia, erythema, vasculitis, nephritis
Levy et al. [8]	20	17	85	arthritis, vasculitis, thrombocytopenia, nephritis
Francioni et al. [9]	12	11	92	arthritis, cytopenia, vasculitis, cerebritis, nephritis
De Pita et al. [10]	5	5	100	fever, arthralgia, asthenia
Gupta et al. (present report)	4	4	100	arthralgia, headache, proteinuria, hypocomplementemia, renal impairment

Discussion

Use of IVIg in lupus nephritis has been infrequent [4, 7–9], even though its successful outcome had been reported earlier. Lupus nephritis warrants aggressive forms of immunosuppressive therapy including drugs like cyclophosphamide and cyclosporine in addition to steroid. Certain severe forms of lupus nephritis will still show progression and fail to remit despite these measures. In this situation one might use drugs like IVIg [14].

Table 4 summarizes the literature on use of IVIg in SLE. It is clear that the majority have used this treatment for extrarenal manifestations with IVIg. Properly randomized studies with proper controls have not been carried out. SLAM scores have been used recently to evaluate clinical efficacy of IVIg. Levy et al. [8] reported 85% response rate using SLAM score after IVIg in 9 patients. As shown in this study certain clinical manifestations like fever, headache and arthralgia may respond better in patients treated with IVIg [8]. IVIg acts via a variety of mechanisms in different diseases. In congenital or acquired forms of hypogammaglobulinemia it substitutes and protects against infection by providing an adequate concentration of IgG. In autoimmune disorders it reduces immune activity by an interaction with Fc receptors on effector cells or by the presence of anti-idiotypic antibodies directed against idiotypes on circulating autoantibodies. IVIg may alter the number of T cell subsets, including an increased number of T suppressor cells. It can also promote solubilization of immune deposits. IVIg may contain neutralizing antibodies against staphylococcal toxin and streptococcal ‘superantigens’, which can bind simultaneously to MHC class I antigens and to the nonantigen binding region of T cell receptors [15].

We report only on patients with severe and resistant lupus nephritis (WHO IV) with persistent and active extrarenal manifestations. We herein define resistance to treatment when there was a lack of response with steroids, intravenous cyclophosphamide pulses and azathioprine and/or cyclosporine for at least 1 year. All 4 subjects showed marked improvement and even disappearance of extrarenal symptoms as shown in table 2. We could not identify any particular extrarenal symptoms, which are more responsive to IVIg in all the study patients. As shown in table 2 and figures 2 and 3, all 4 patients had normalization of serum creatinine and serum albumin. In addition there were significant decreases in urinary protein excretion even though they remained above normal values. It is difficult to quantify the renal response to IVIg, but repeat biopsies done in 2 subjects did demonstrate marked diminution in lupus activity indices.

In 2 subjects repeat renal histology could not be studied due to lack of consent. Significant decrease in proteinuria, improvement in serum albumin levels and renal symptomatology as shown in table 2 and figure 2 denote success of IVIg treatment. In addition these subjects insisted on continuing this therapy due to marked improvement in their clinical status. Reduction of antibody levels and normalization of complement levels were reported with IVIg recently, but it was not consistent for several antibodies measured in the same patients [16]. We could not observe any significant serological improvement despite commendable clinical biochemical and histological remission. A larger group of patients is required in order to find more consistent correlation between autoantibodies and complements with response to IVIg therapy.

Treatment with IVIg is expensive and it is not indicated as a first-line therapy. Its use should be reserved for patients with resistant lupus nephritis with severe extra-renal manifestations. There are no proper guidelines for withdrawal of IVIg therapy in these patients. However, we recommend that withdrawal may be considered once the patients achieve and are able to maintain symptom-free periods along with biochemical and immunological remission for a period of more than 1 year.

Standard first-line therapy of AIHA are corticosteroids. It is reported to respond in up to 80% of cases within 10 days of treatment [17, 18]. Second-line therapy includes splenectomy or other immunosuppressive drugs such as azathioprine. IVIg may be considered in subjects resistant to conventional forms of therapy. Our patient continued to have relapses of hemolysis despite adequate doses of steroid and azathioprine. Splenectomy was deferred and IVIg was started. He showed excellent response with this treatment with rise in hemoglobin and absence of hemolytic crises. IVIg is reported to have a major role

in patients with warm type of AIHA that does not respond to corticosteroid similar to our subject [19]. Previous reports of lack of beneficial effect of IVIg in AIHA could be due to use of smaller doses [20]. Lack of response to conventional doses has been attributed in certain cases to the expansion of reticuloendothelial systems that is seen in patients with AIHA [21].

Conclusion

IVIg has shown excellent therapeutic effect as an additional drug in the treatment of renal and extra-renal manifestations of SLE, which are resistant to other modalities of treatment.

Acknowledgment

We wish to express our sincere thanks to Mr. George Varughese for the help rendered in the preparation of the manuscript.

References

- 1 Balow JE, Boumpas DT, Austin HA 3rd: New prospects for treatment of lupus nephritis. *Semin Nephrol* 2000;20:32–39.
- 2 Kazatchkine MD, Merell A (eds): *Intravenous Immunoglobulin: Research and Therapy*. New York, Parthenon, 1996.
- 3 Shoenfeld Y, Krause I: Immunosuppression and immunomodulation of experimental models of systemic lupus erythematosus and antiphospholipid syndrome. *Transplant Proc* 1996;28:3096–3098.
- 4 Lin CY, Hsu HC, Chiang H: Improvement of histological and immunological change in steroid and immunosuppressive drug-resistant lupus nephritis by high-dose intravenous gamma globulin. *Nephron* 1989;53:303–310.
- 5 Corvetta A, Della Bitta R, Gabrielli A: Use of high-dose intravenous immunoglobulin in systemic lupus erythematosus: Report of three cases. *Clin Exp Rheumatol* 1989;7:295–299.
- 6 Maier WP, Gordon DS, Howard RF, Saleh MN, Miller SB, Lieberman JD, Woodlee PM: Intravenous immunoglobulin therapy in systemic lupus erythematosus-associated thrombocytopenia. *Arthritis Rheum* 1990;33:1233–1239.
- 7 Schroeder JO, Zeuner RA, Euler HH, Löffler H: High dose intravenous immunoglobulin in systemic lupus erythematosus: Clinical and serological results of a pilot study. *J Rheumatol* 1996;23:71–75.
- 8 Levy Y, Sherer Y, Ahmed A, Langevitz P, George J, Fabbrizzi F, Terryberry J, Meissner M, Lorber M, Peter JB, Shoenfeld Y: A study of 20 SLE patients with intravenous immunoglobulin: Clinical and serologic response. *Lupus* 1999;8:705–712.
- 9 Francioni C, Galeazzi M, Fioravanti A, Gelli R, Megale F, Marcolongo R: Long-term ivIg treatment in systemic lupus erythematosus. *Clin Exp Rheumatol* 1994;12:163–168.
- 10 De Pita O, Bellucci AM, Ruffelli M, Girardelli CR, Puddu P: Intravenous immunoglobulin therapy is not able to efficiently control cutaneous manifestations in patients with lupus erythematosus. *Lupus* 1997;6:415–417.
- 11 Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–1277.
- 12 Liang MH, Socher SA, Larson MG, Schur PH: Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1989;32:1107–1118.
- 13 Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Bombardier C, Isenberg D, Kalunian K, Liang MH, Maddison P, Nived O: Sensitivity to change of 3 systemic lupus erythematosus disease activity indices: International validation. *J Rheumatol* 1994;21:1468–1471.
- 14 Jayne DR, Davies MJ, Fox CJ, Black CM, Lockwood CM: Treatment of systemic vasculitis with pooled intravenous immunoglobulin. *Lancet* 1991;337:1137–1139.
- 15 Kuruskall MS, Mandel BF: Intravenous immunoglobulin-drug information. UP to date 1999; 800:6362–6374.
- 16 Jordan SC: Intravenous gamma-globulin therapy in systemic lupus erythematosus and immune complex disease. *Clin Immunol Immunopathol* 1989;53:S164–S169.
- 17 Boletis JN, Ioannidis JP, Boki KA, Moutsopoulos HM: Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. *Lancet* 1999;354:569–570.
- 18 Collins PW, Newland AC: Treatment modalities of autoimmune blood disorders. *Semin Hematol* 1992;29:64–74.
- 19 Otten A, Bossuyt PM, Vermeulen M, Brand A: Intravenous immunoglobulin treatment in hematological diseases. *Eur J Haematol* 1998;60: 73–85.
- 20 Mueller-Eckhardt C, Salama A, Mahn I, Kiefel V, Neuzner J, Graubner M: Lack of efficacy of high-dose intravenous immunoglobulin in autoimmune hemolytic anemia: A clue to its mechanism. *Scand J Haematol* 1985;34:394–400.
- 21 Bussell JB, Cunningham-Rundles C, Abraham C: Intravenous treatment of autoimmune hemolytic anaemia with very high dose gamma globulin. *Vox Sang* 1986;51:264–269.