HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN FOR SYSTEMIC LUPUS ERYTHEMATOSUS WITH LUPUS NEPHRITIS AND ASSOCIATED STUDIES – CASE REPORT

Lim SK , Tan SY
Renal Unit , Department of Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

ABSTRACT: Systemic lupus erythematosus (SLE) is one of the commonest systemic autoimmune diseases that can present with variable clinical manifestations. Intravenous Immunoglobulin (IVIG) has been used as a salvage therapy for severe lupus with encouraging results though there is yet randomised trial to support the usage. This report highlights the efficacy and safety of high dose IVIG in SLE patients with multi-organ involvement particularly lupus nephritis. We also reviewed the literature on the usage of IVIG for lupus nephritis. However, more studies are needed to further clarify the optimal therapeutic dosage and regime for IVIG and to identify the group of patients who might benefit the most from this expensive therapy. *(JUMMEC 2007; 10(2):51-56)*

KEYWORDS: Systemic lupus erythematosus, lupus nephritis, Intravenous Immunoglobulin

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder with variable clinical manifestations that can range from mild clinical findings to life-threatening condition. The conventional treatment for SLE includes steroids and cytotoxic agents such as cyclophosphamide, azathioprine, cyclosporine and newer agent, mycophenolate mofetil. These agents can be very effective in suppressing SLE activity but can also result in severe infection due to immunosuppression. Intravenous immunoglobulin (IVIG) is a standard treatment for various immunodeficiency states and some autoimmune disease such as immune thrombocytopenic purpura (ITP), Guillain-Barre disease, polymyositis and Kawasaki's disease. This expensive drug has been used as a rescue therapy to treat SLE for the past 20 years with encouraging results. We reported three cases of SLE with lupus nephritis and multi-organ involvement that were treated with high dose IVIG with excellent response.

Case Reports

Case 1

Miss NH is a 17-year-old girl who was found to have SLE in 2003 when she presented with autoimmune haemolytic anaemia. She was treated with prednisolone and Azathioprine with satisfactory response. She was diagnosed to have lupus nephritis in April 2005 with renal biopsy confirmed diffuse proliferative glomerulonephritis (DPGN). She then deteriorated with spiking temperature, worsening renal function and severe abdominal pain with profuse watery diarrhea. She developed severe sepsis and was treated empirically as spontaneous bacterial peritonitis in addition to active SLE with multi-organ involvement, i.e., lupus nephritis with renal failure, serositis with pleural effusion and pericardial effusion as well as possible mesenteric vasculitis.

She was managed in the intensive care unit and was commenced on continuous renal replacement therapy. In view of concomitant sepsis and active lupus, IVIG was commenced at 0.4 g/kg/day for five days (total dose of 2 g/kg). Her condition stabilised and she was transferred to the normal ward after one week but was still dialysis-dependent. She developed status epilepticus nine days later which needed multiple anti-epileptic agents to control the seizure. Biochemistry results, CT brain and lumbar puncture excluded infective and metabolic cause of the status epilepticus. She was treated as lupus cerebritis and was commenced on therapeutic plasma exchange. She responded well to the treatment with cessation of the seizure and renal

Correspondence :
Lim Soo Kun
Department of Medicine,
Faculty of Medicine,
University of Malaya,
50603 Kuala Lumpur, Malaysia.
email: sookun73@yahoo.com

function continued to improve till off dialysis after three weeks. She was commenced on mycophenolate mofetil at the dose 2 g per day after completing six monthly cycle of IVIG. She is currently well with complete remission of the SLE. The renal function remained normal with latest serum creatinine of 60μmol/L and she has no residual neurological deficit.

Case 2

Miss NSC was found to have SLE at the age of fifteen when she presented with skin rashes, arthritis, leucopenia and thrombocytopenia. She was initially treated with oral prednisolone and hydroxychloroquine with satisfactory response. Five years later, she developed class IV lupus nephritis. She achieved complete remission after a course of oral cyclophosphamide. She could not tolerate Azathioprine due to leucopenia and was commenced on mycophenolate mofetil (Cellcept) with excellent response.

However, she stopped taking the medications due to financial reasons and was presented with features of active SLE nine months later with leg swelling, facial puffiness, multiple joint pain, fever and thrombocytopenia. She was given pulse methylprednisolone with total dose of 1.5 grams but developed generalised tonic-clonic seizure and acute confusional state. All the electrolytes were normal and CT scan of brain did not reveal any intracranial lesion. At the same time, the renal function deteriorated very rapidly requiring dialysis support. Therefore, diagnosis of active SLE with possible cerebral lupus, lupus nephritis with rapidly progressive glomerulonephritis (RPGN) and thrombocytopenia was made. In view of the spiking temperature and possible concurrent infection, IVIG was started at 0.4g/kg/day for five days (total dose of 2g/kg).

She continued to have high blood pressure with persistent headache and blurred vision. MRI brain revealed sagittal sinus thrombosis. The thrombophilia screen was negative. Anticardiolipin antibody and lupus anticoagulant were also not suggestive of antiphospholipid syndrome. Lumbar puncture was also normal. She was commenced on anticoagulation. Her renal function stabilised after the IVIG and she managed to come off dialysis after one week with serum creatinine ranged 200 - 240μmol/L. The platelet count also normalised later and she was maintained seizure-free with antiepileptics. She continued to receive IVIG for another three monthly cycles before converting to mycophenolate mofetil. She remained well and the serum creatinine continued to improve and ranged 160-180 μmol/L on last follow-up. Renal biopsy which was performed after she completed the warfarin therapy revealed class IV lupus nephritis with evidence of chronicity.

Case 3

Miss NW, 22-year-old lady, was diagnosed to have SLE in 2003 with nephrotic-nephritic syndrome and positive SLE serology. Renal biopsy confirmed focal proliferative glomerulonephritis with membranous changes (Class III and V disease). She achieved remission after prednisolone and Azathioprine. She was advised to have a repeat renal biopsy at the end of 2006 when was found to have increased proteinuria and active urine sediments. Unfortunately, she was not keen and the prednisolone dose was stepped up during the review.

A month later, she presented after being unwell and febrile for three weeks. She developed episodes of seizure and was ventilated for airway protection. Further investigations revealed that she has active SLE with multi-organ involvement which include lupus nephritis with renal failure, pancytopenia, extensive vasculitic lesions over the trunk and limbs and likely cerebral lupus which caused the seizures. MRI revealed cerebral atrophy which was not consistent with her age but no vasculitic lesion in the brain and no evidence of transverse myelitis. Lumber puncture was not performed without the consent from the parents.

Intravenous methylprednisolone was given but was withheld after two doses due to spiking temperature. IVIG was commenced at 0.8g/kg/day for four days (total dose of 3.2g/kg). At the same time, her kidney function worsened and was commenced on continuous renal replacement therapy. She improved very slowly and needed prolonged ventilation for almost a month. Her renal function also started to improve after the second dose of IVIG three weeks later and she managed to come off dialysis after being dialysis-dependent for 36 days.

Unfortunately, she was found to have tetraplegia with no bladder or bowel involvement after being extubated. Nerve conduction study showed axonal peripheral neuropathy which was not conclusive. Her neurological status improved very slowly but was encouraging. At the current state, she is ambulating with support and is independent on activities of daily living. In view of the significance improvement, the IVIG was continued at 3.2g/kg for total of four cycles before changing to mycophenolate mofetil as maintenance therapy. Renal biopsy later confirmed Class IV lupus nephritis with crescent formation. She is currently in complete remission with normal renal function.

Literature Review

Intravenous immunoglobulin (IVIG) has been used to treat Systemic lupus erythematosus (SLE) for various indications for decades which include lupus nephritis, cerebral lupus with encephalitis, neuropsychiatric lupus, immune thrombocytopenia or autoimmune haemolytic anaemia, antiphospholipid syndrome, pneumonitis, serositis and vasculitis. The most extensive experience is with lupus nephritis. However, the usage is mainly based on case reports and case series. We reviewed about 16 reports/series which used IVIG in lupus nephritis of various classes. The overview is presented in Table 1.

The most common indication to use IVIG in most of the reports is as a salvage therapy for severe active lupus when the patients do not response to conventional therapy or when there is concurrent active disease and sepsis. Various IVIG doses and regime has been used in different reports. The commonest dosage regime is 0.4g/kg/day for five days or total dose of 2g/kg which is most probably based on the experience of IVIG in treatment of other autoimmune disorders such as Guillain-Barre syndrome and ITP. The total courses given ranged from one to twenty-four. Overall, there was no conclusive evidence to suggest the optimal therapeutic dosage and regime.

There was only one randomised trial by Boletis and coworkers (1999) who studied the use of IVIG as maintenance therapy in proliferative glomerulonephritis (1). All the patients were treated with prednisolone and cyclophosphamide for six months before being randomised to cyclophosphamide or IVIG as maintenance therapy. Five patients were treated with IVIG 0.4g/kg body weight monthly for 18 months and nine patients were treated with cyclophosphamide 1g/m2 every two months for six months and every six months for one year. IVIG was found to be safe and as efficacious as cyclophosphamide to maintain the disease activity. However, the cost effectiveness of the above approach needs further evaluation.

The first report came from Sugisaki in 1982 who reported the use of IVIG in three patients with lupus nephritis with 100% improvement in proteinuria (2). Most of the experience on use of IVIG in lupus nephritis was reported in 1990s. Monova had the largest clinical experience with IVIG in the recent years involving 116 patients with biopsy-proven glomerulonephritis (3). Among those, fifty-eight patients had lupus nephritis with varying classes from class II to V. Among the eighteen patients with proliferative glomerulonephritis (Class IV), twelve achieved partial or complete remissions, two was dialysis-dependent and five died. Similarly, the IVIG dose used was much lower i.e. 0.255g/kg body weight.

In summary, the above reports suggested that IVIG is a safe and efficacious therapy for lupus nephritis of varying classes. Yet, many questions remained unanswered. Controlled studies on the use of IVIG in SLE and lupus nephritis in particular are very limited. Secondly, the dosage and regime used in various reports has been variable. In view of the high cost of the therapy, further study to determine the appropriate therapeutic indications and the optimal dosage and regime would be very essential.

Discussion

The three patients who were presented above had severe active SLE with multi-organ involvement which include Class IV lupus nephritis, neurological and haematological involvement. Table 2 gives an overview of patients' details, treatment and outcome. One of the main indications for IVIG in these three cases is concomitant sepsis and active SLE because of its immunomudulatory effects. As in other autoimmune diseases, the exact mechanism of action of IVIG in SLE is unclear. Some investigators demonstrated that gamma globulins solubilised glomerular immune deposits in lupus nephritis patients (4). Sugisaki and Lin has reported a marked reduction in immune deposits along glomerular capillary walls on follow-up renal biopsy after IVIG treatment in 1980's (2,5). However, the direct action of IVIG on glomerular immune complexes needs further investigation.

All the three patients showed marked improvement in renal function after IVIG therapy and managed to come off dialysis even though one patient (NSC) was dialysis-dependent for more than one month. The proteinuria started to reduce after the first course with normalisation of the serum albumin. This process usually takes weeks to months. Haematological complications seem to respond faster after IVIG therapy. We used IVIG dose of 2.0g/kg for the first two cases, which is the commonest dosing used in the literature. This experience was extrapolated from usage of IVIG in other conditions such as Kawasaki disease, Guillain-Barre syndrome and immune thrombocytopenic purpura (ITP). Nevertheless, the optimal dose and regime for IVIG in SLE remained unanswered. For patient NW, higher dose of 3.2g/kg was used because she was more ill at presentation.

The three patients tolerated the IVIG therapy well with no commonly reported side effects such as anaphylactoid reactions, low grade fever, backache, nausea, excessive sweating, headache or hypotension. Some has been concerned on the usage in SLE patients when Barron (1992) reported three patients who developed exacerbation or new onset of renal disease after IVIG therapy (6). IVIG induced acute renal failure

Table 1. Literature review of IVIG in lupus nephritis.

Year	Author	Type of study	Pt. No	WHO Class of LN	IVIG regime	Improved renal function	Improved proteinuria
1982	**Sugisaki (2)**	Case report	3	NS	Total dose 30g	NS	3/3
1989	**Lin (5)**	Case series	9	WHO IV 5 WHO IV+V 2 WHO V 2	2g/kg x 1-2 courses	IV- 5/5 IV+V- 2/2 V- 2/2 minor improvement	9/9
1989	**Corvetta (9)**	Case report	1	IV	1.2g/kg x 1 course	Deteriorated due to ATN	NS
1990	**Akashi K. (10)**	Case report	2	WHO IIb x 1 WHO III x 1	0.6-2.25g/kg monthly x 2-3 courses	NS	2/2
1992	**Oliet A. (11)**	Case report	1	IV	2g/kg x 1 course	Normal renal function	1/1
1993	**Winder A. (12)**	Case report	1	V	2g/kg x 1 course	1/1	1/1
1994	**Francioni C. (13)**	Case series	5	III & IV	2g/kg monthly x 6-24 courses	5/5	5/5
1995	**Welch *et al*. (14)**	Case report	1	IV	1g/kg monthly x 6 courses	Normal renal function	1/1
1995	**Welcker and Helmke (15)**	Case series	7	NS	Total dose 30g x 1 and Immunoadsorbtion	NS	NS
1999	**Arahata H. (16)**	Case report	1	IV	Total dose 62.5g	1/1	1/1
1999	**Boletis JN (1)**	RCT	5	WHO III 4 WHO IV 1	0.4g/kg monthly x 18 courses	Maintained remission	Maintained remission
1999	**Levy Y. (17)**	Case series	5	NS	2g/kg x 1-6 courses	NS	4/5
2000	**Levy Y. (18)**	Case series	7	WHO IV- 3 WHO V- 2 No biopsy- 2	2g/kg x 1-6 courses	NS	7/7
2000	**Meissner M. (19)**	Case report	1	NS	2.8g/kg x 1 course	Normal renal function	1/1
2002	**Monova D. (3)**	Case series	58	WHO II 16 WHO III 6 WHO IV 18 WHO V 18	0.255g/kg x 1-28 courses	CR 14 PR 27 Dialysis 8 Death 9	NS
2005	**Sevil Kamali (20)**	Case series	4	NS	2g/kg monthly x 1-6 courses	2/4	2/4

** LN lupus nephritis. ATN acute tubular necrosis. CR complete remission. PR partial remission. NS not specified. RCT randomised controlled trial.*

Table 2. Patients' characteristics, treatment details and outcome.

	NH	NSC	NW
Age	17	29	22
Age at presentation(year)	13(2003)	15(1993)	16(2000)
Race	Malay	Chinese	Malay
Lupus history - Organ involvement	4 years of SLE	4 years of SLE	6 years of SLE
1. Skin rash	Yes	Yes	Yes
2. Arthritis	Yes	Yes	Yes
3. Lupus nephritis	Class IV	Class IV	Class IV
4. Neurological	Cerebral lupus Depression	Sagittal sinus thrombosis	Cerebral lupus
5. Haematological	Autoimmune haemolytic anaemia	Leucopenia, thrombocytopenia	Thrombocytopenia
6. Serositis	Pleural effusion	Nil	Nil
7. Vasculitis	Pericardial effusion Mesenteric vasculitis (possible)	Nil	Skin Vasculitis
Associated antiphospholipid syndrome	Nil	Nil	Nil
Duration of dialysis dependent	21 days	7 days	32 days
Immunosuppression before relapse	Prednisolone & Azathioprine	Prednisolone	Prednisolone & Azathioprine
IVIG regime & dose	2g/kg, completed 6 monthly cycle	2g/kg, completed 4 monthly cycles	3.2g/kg, completing 4 3-weekly cycle
Outcome	Normal renal function Proteinuria resolved No neurological deficit, no depression	Mild renal impairment Proteinuria reduced more than 50% No neurological deficit	Normal renal function Proteinuria resolved Paraparesis (improving) Complete resolution of skin vasculitis
Immunosuppression after IVIG	Prednisolone & mycophenolate mofetil	Prednisolone & mycophenolate mofetil	Prednisolone & mycophenolate mofetil

is rare but potentially serious complication especially in our patients who presented with renal failure. It is also important to note that the renal complication is most probably infusion rate-dependent rather than dose-dependent (7). It was initially thought to be an immunological process when newly formed nephritogenic circulating immune complexes formed by anti anti-idiotype antibody deposit in kidney causing glomerular damage (8). Nowadays, the recognised mechanism of acute renal failure after IVIG therapy is 'osmotic nephrosis'. Large amount of sucrose used as a preservative in some IVIG products is the most probable culprit though the complication might occur even in IVIG not containing sucrose. As in contrast nephropathy, the higher risk is in patients with pre-existing renal failure, elderly, diabetics, volume depletion and concomitant use of nephrotoxic agents or diuretics.

Conclusion

Our report suggested IVIG as a safe and effective rescue therapy for SLE with multi-organ involvement. The decision to use IVIG in SLE patients is easier in severe clinical situations. Higher dosage and prolonged regime might confer more benefits. More studies are needed to determine the group of patients who might benefit the most from IVIG therapy as well as the optimal IVIG dosage and regime.

References

1. Boletis JN, Ioannidis JPA, Boki KA, *et al*. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. *Lancet 1999*; 354:569-70.
2. Sugisaki T, Shiwachi S, Yonekura M, *et al*. High dose intravenous gammaglobulin for membranous nephropathy, membranoproliferative glomerulonephritis and lupus nephritis. *Fed Proc 1982*; 41:692.
3. Monova D, Belovezhdov N, Altunkova I, *et al*. Intravenous immunoglobulin G in the treatment of patients with chronic glomerulonephritis: clinical experience of 15 years. *Nephron 2002*; 90:262-66.
4. Tomino Y, Sakai H, Takaya M, *et al*. Solubilisation of intraglomerular deposits of IgG immune complexes by human sera or gammaglobulin in patients with lupus nephritis. *Clinical Experiment in Immunology 1984*; 58:42-8.
5. 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*; 53:303-10.
6. Barron KS, Sher MR, Silverman ED. Intravenous immunoglobulin therapy: magic or black magic. *J Rheumato 1992*; 19(S33):94-97.
7. Stahl M, Schifferli JA. The renal risks of high dose intravenous immunoglobulin treatment. *Nephrol Dial Transplant 1998*; 13:2182-85.
8. De Vita S, Ferraccioli GF, Di Poi E, *et al*. High dose intravenous Immunoglobulin therapy for rheumatic diseases: clinical relevance and personal experience. *Clin Exp Rheumatol 1996*; 14:S85-92.
9. Corvetta A, Della Bitta R, Gabrielli A, *et al*. Use of high-dose intravenous immunoglobulin in systemic lupus erythematosus: report of three cases. *Clin Exp Rheumatol 1989*; 7:295-99.
10. Akashi K, Nagasawa K, Mayumi T, *et al*. Successful treatment of refractory systemic lupus erythematosus with intravenous immunoglobulin. *J Rheumatol 1990*; 17:375-79.
11. Oliet A. High-dose intravenous gammaglobulin in systemic lupus erythematosus. *Nephron 1992*; 62:465
12. Winder A, Molad Y, Ostfeld I, *et al*. Treatment of systemic lupus erythematosus by prolonged administration of high dose intravenous immunoglobulin: report of two cases. *J Rheumatol 1993*; 20:495-98.
13. Francioni C, Galeazzi M, Fioravanti A, *et al*. Long term intravenous immunoglobulin treatment in systemic lupus erythematosus. *Clin Exp Rheumatol 1994*; 12:163-68.
14. Welch TR, McAdams AJ, Beischel LS. Glomerulonephritis associated with complete deficiency of the fourth component of complement: response to intravenous immunoglobulin. *Arthritis Rheum 1995*; 38:1333-37.
15. Welcker M, Helmke K. Immunologic therapy for glomerulonephritis with combined immunoadsorbtion and IVIG therapy. *Immunitat Infekt 1995*; 23:140-41.
16. Arahata H, Migita K, Izumoto H, *et al*. Successful treatment of rapidly progressive lupus nephritis associated with anti-MPO antibodies by intravenous immunoglobulin. *Clin Rheumatol 1999*; 18:77-81.
17. Levy Y, Sherer Y, George J, *et al*. Intravenous immunoglobulin treatment of lupus nephritis. *Semin Arthritis Rheum 2000*; 29:321-27.
18. Levy Y, Sherer Y, Ahmed A, *et al*. A study of twenty SLE patients with intravenous immunoglobulin-clinical and serologic response. *Lupus 1999*; 8:705-12.
19. Meissner M, Sherer Y, Levy Y, *et al*. Intravenous immunoglobulin therapy in a patient with lupus serositis and nephritis. *Rheumatol Int 2000*; 19:199-200.
20. Kamali S, Cefle A, Sayarlioglu M, *et al*. Experience with monthly, high dose, intravenous immunoglobulin therapy in patients with different connective tissue diseases. *Rheumatol Int. 2005*; 25:211-14.