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Intravenous Immunoglobulin in the Therapeutic Armamentarium of Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

Rajalingham Sakthiswary, MRCP, and David D'Cruz, FRCP

Abstract: Prepared from the plasma of thousands of blood donors, therapeutic intravenous immunoglobulin (IVIg) mostly consists of human polyspecific immunoglobulin G (IgG). The use of IVIg in systemic lupus erythematosus (SLE) is still considered experimental without any clear indications.

The purpose of this systematic review is, therefore, to evaluate the available evidence to determine the therapeutic role of IVIg in SLE.

A comprehensive, computerised search was performed in the MEDLINE (Pubmed), Scopus, EMBASE, and Cochrane controlled trials.

The study eligibility criteria were randomized controlled trials, and prospective and retrospective observational studies that examined the efficacy of IVIg in adult patients with SLE who were considered the participants.

IVIg therapy was the mode of intervention in these patients.

Data abstracted included the study design, study population, changes in the disease activity scores (Systemic Lupus Erythematosus Disease Activity Index, Systemic Lupus Activity Measure, and Lupus Activity Index-Pregnancy), steroid dose, complement levels, autoantibodies, and renal function. Thereafter, data analysis established statistical procedures for meta-analysis.

Thirteen studies (including 3 controlled and 10 observational) were eligible for inclusion. There was significant reduction in the SLE disease activity scores with IVIg therapy with a standard mean difference of 0.584 ($P = 0.002$, 95% confidence interval [CI] 0.221–0.947). In terms of rise in complement levels, the response rate was 30.9% ($P = 0.001$, 95 CI 22.1–41.3). The effects of IVIg on other clinical outcome measures including anti-double-stranded DNA, antinuclear antibody, average steroid dose, and renal function could not be determined because of the limited numbers of trials.

The limitations of this review were lack of well-designed controlled trials with adequate sample size on the use of IVIg in SLE.

In conclusion, the use of IVIg is associated with significant reduction in SLE disease activity and improvement in complement levels.

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Abbreviations: ANA = antinuclear antibody, antidsDNA = anti-double-stranded DNA, CI = confidence interval, ESR = erythrocyte sedimentation rate, IVIg = intravenous immunoglobulin, LAI-P = Lupus Activity Index-Pregnancy, SLAM = Systemic Lupus Activity Measure, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

INTRODUCTION

Therapeutic preparations of intravenous immunoglobulin (IVIg) are derived from the plasma of healthy individuals by cold ethanol fractionation. The majority of commercial preparations of IVIg predominantly consist of polyclonal immunoglobulin G (IgG) (>90%). IgM, IgA, and traces of soluble molecules including human leukocyte antigen are also present in small quantities.[1] IVIg, which was formulated in the 1960s, was initially used as a replacement therapy in immunodeficiency disorders.[2] It was not until the 1980s that IVIg was tested in the treatment of systemic lupus erythematosus (SLE).[3,4]Although the exact mechanism of action of IVIg as an immunomodulator remains unclear, it has been postulated that the Fc portion of the IgG is the key orchestrator in this regard. The Fc portion binds to the Fc receptors of the macrophages that, in turn, inhibits the binding of the autoantibody-coated targets to these receptors. Moreover, IVIg exerts its therapeutic properties by inhibiting the formation of membrane attack complex through the binding of the Fc portion to the complement components C3b and C4b.[5]

To date, in SLE, there are only 4 drugs, namely, hydroxychloroquine, corticosteroids, belimumab, and aspirin, approved by the Food and Drug Administration (FDA). As such, the use of IVIg in SLE remains off-label and unlicensed. Many clinicians are unsure of the role of IVIg in SLE, especially in the present era of biologic therapies. Although IVIg may not be necessary in patients with mild SLE, who are well controlled with conventional immunosuppressants, most clinicians would consider IVIg as an option in patients who are either refractory to or have contraindications for standard therapies such as cyclophosphamide, mycophenolate mofetil, and azathioprine.

In the last few decades, several clinical studies, mostly uncontrolled, have examined the effects of IVIg in SLE, with variable results. Hence, the main objective of this systematic review is to summarize the results of these studies and evaluate the therapeutic role of IVIg in SLE.

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From the Department of Medicine (RS), Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Cheras, Malaysia; and Louise Coote Lupus Unit (DD), Gassiot House, St Thomas' Hospital, London, United Kingdom
Correspondence: Rajalingham Sakthiswary, Universiti Kebangsaan Malaysia, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur (e-mail: sakthis5@hotmail.com).
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METHODOLOGY

Search Strategy and Study Selection

The MEDLINE, EMBASE, SCOPUS, ISI Web of Science, and Cochrane controlled trials register were searched using the search terms "systemic lupus erythematosus," "lupus," and "SLE" (both as medical subject heading and free text). These were combined using the set operator "and" with studies identified with the terms "intravenous immunoglobulin" and "IVIg." This search was completed by using standard Internet search engines. No date restrictions were applied in the selection process of the relevant articles. When faced with insufficient or incomplete data, authors of the respective studies were directly contacted through e-mail. All clinical studies including randomized controlled trials, and prospective and retrospective observational studies that examined the effects of IVIg in adult SLE patients were eligible for inclusion.

Other inclusion criteria included:

1. Diagnosis of SLE based on either American College of Rheumatology criteria or the treating physician's opinion.
2. Treatment with intravenous immunoglobulin.
3. Administration of placebo or standard therapy for patients randomized to the control arm in case–control studies.

The Abstract of the studies identified by initial screening were scrutinized for appropriateness before retrieving the full text of the articles. The bibliographies of relevant studies were thoroughly checked to get additional references. Moreover, relevant unpublished trials, conference proceedings, and trial registries were identified from the references of these studies. Only articles that were published in English were considered. Ethical approval was not necessary for this meta-analysis as the results for publication only involved de-identified pooled data from individual studies that have received ethics approval. Figure 1 summarizes the algorithm followed for the selection of studies.

Data Extraction

The following data were extracted from all studies included in this systematic review: study design, study population, sample size, dose, and duration of IVIg therapy. The details of the control arm employed were recorded for all the controlled trials. Outcome measures that were studied included:

1. disease activity scores (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI], Systemic Lupus Activity Measure [SLAM], and Lupus Activity Index-Pregnancy [LAI-P]),
2. steroid dose reduction,
3. change in the levels of autoantibodies (anti-double-stranded DNA [anti-dsDNA], antinuclear antibody [ANA], anti-SSA, and anti-SSB),
4. change in complement 3 (C3) and 4 (C4) levels,
5. renal function (proteinuria, creatinine).

Data Synthesis and Statistical Analysis

Data were pooled from controlled and uncontrolled studies using a random effects model for a more conservative estimate of the effects of IVIg therapy on disease activity scores and complement levels. This model allows for heterogeneity across the studies.[6] The above outcome measures were expressed as standard difference in means or event rate with 95% confidence intervals. As there were only 2 studies with controls,[7,8] the control groups were not included in the statistical analysis.

The remaining outcome variables (steroid dose, autoantibodies, renal function) were not statistically analyzed owing

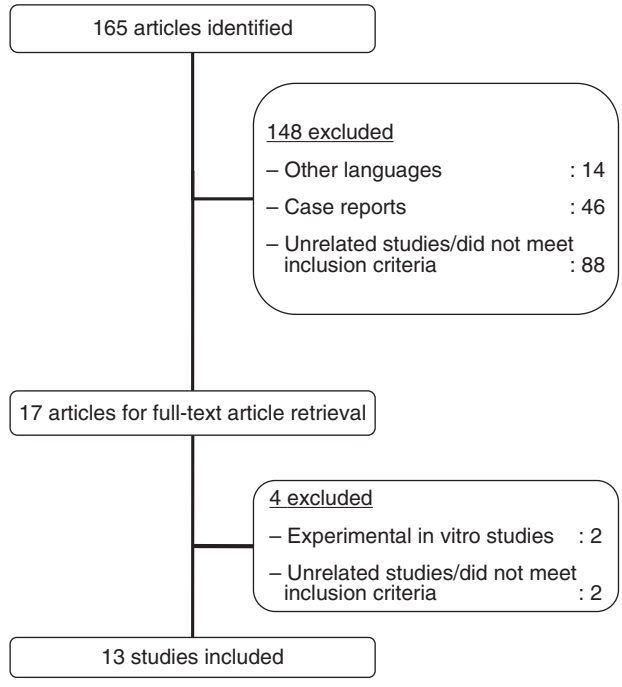

FIGURE 1. Algorithm for selection of studies in the systematic review.

to the small numbers of studies and unavailability of data on mean values or response rate. Heterogeneity was statistically studied using the I^2 test, with values of >50% being deemed indicative of heterogeneity.[9] Comprehensive meta-analysis software version 2.0 statistical programme was used for data analysis and generating the forest plots.

RESULTS

A total of 13 studies met the eligibility criteria and were included in this systematic review[7,8,10–20] (see Table 1). These included 1 randomized controlled trial,[7] 2 nonrandomized controlled trial,[8,20] 6 prospective observational studies,[10–13,15,19] and 3 retrospective studies.[16–18] Among the selected studies, only 3 had employed controls.[7,8,21] The patients in the control arm were either on corticosteroids and nonsteroidal anti-inflammatory drugs[8] or cyclophosphamide as the comparator drug.[7]

Majority of the studies (7/13) originated from Europe[7,8,11,12,15,18,21] followed by Asia (5/13)[13,14,16,17,19] and the United States (1/13).[10] Of note, all 4 studies from Asia were conducted in Israel. To date, there are no studies in this regard from Africa or Australia. These studies were all published between 1989 and 2013, and the duration of the individual studies ranged from 1 to 24 months. The sample sizes of the individual studies ranged from 7 to 132 subjects. The dose of IVIg per course of treatment used in most of the studies was 400 mg/kg/d over 5 days. Across the studies, the study populations were rather heterogenous in terms of clinical manifestation of SLE. Five studies involved subjects with lupus nephritis,[7,11,14,19,20] 2 were on hematological,[10,11] and 1 was on cutaneous involvement[15] in SLE. Most studies did not clearly state the specific numbers and reasons for dropouts.

Effect of IVIg on SLE Disease Activity

Six studies, with a total of 261 subjects, investigated the effect of IVIg on disease activity scores.[8,12,13,16,17,20,21] The disease activity scores used as outcome measures included SLEDAI,[16,17] SLAM,[12,13] and LAI-P.[8] The disease activity scores significantly decreased in all of the studies. An appreciable decline in the scores was seen as early as 6 weeks following the IVIg therapy.[12]

Figure 2 shows the forest plot of the aforementioned studies. The pooled analysis of these studies suggests that IVIg is associated with significant reduction in disease activity scores on random effects model with a standard mean difference of 0.584 ($P = 0.002$, 95% confidence interval [CI] 0.221–0.947). The inter-study heterogeneity test yielded a statistical significance of $P = 0.003$, with I^2 of 78.42%.

IVIg as a Steroid-Sparing Agent

Three studies, with a total of 45 subjects, investigated the effect of IVIg as a steroid-sparing agent.[7,13,17] Levy et al[13] and Zandman-Goddard et al[17] reported a significant reduction in the average daily dose of corticosteroids. The pooled data from the above studies demonstrated a mean reduction of 17.95 mg/d in the dose of corticosteroids with IVIg therapy. Boletis et al[7] compared the cumulative steroid dose between the IVIg and the cyclophosphamide-treated patients. The cyclophosphamide arm tended to have a higher dose (4719 vs 3334 mg), but this difference, however, did not reach statistical significance.

Effect of IVIg on Complement Levels

Eight studies investigated the changes in complement levels.[8,10–13,16,19,21] The results were rather conflicting. Francioni et al,[11] Perricone et al,[8] and Sherer et al[16] reported a rising trend in complement levels with IVIg therapy whereas Maier et al,[10] Monova et al,[20] and Schroeder et al[12] demonstrated no changes in this parameter. Levy et al[13] surprisingly found a significant decline in C4 levels with the above treatment ($P = 0.007$).

The changes in the complement levels were reported as number of responders (subjects with increment in complement levels)/total number of subjects on IVIg therapy in 6/8[8,10–12,16,19] of the studies with a total of 114 patients. The results showed a pooled response rate of 30.9% ($P = 0.001$, 95% CI 22.1–41.3), using the random effects model. The heterogeneity test yielded a value of $I^2 = 72.66\%$ that was statistically significant ($P = 0.006$) (Figure 3).

Effect of IVIg on Autoantibodies

Four studies investigated the changes in the quantitative values of ANA and antidsDNA with IVIg therapy.[8,12,13,20] Two out of 4 of the studies[12,13] demonstrated no significant changes in the levels of ANA. AntidsDNA, on the other hand, showed significant reduction in 3/4 studies.[8,12,20] Two of the studies looked into the serial levels of anti-SSA and

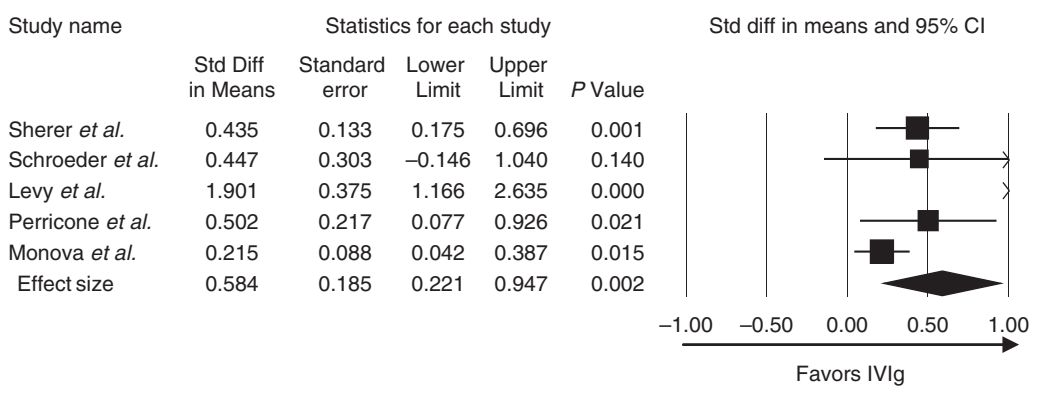

FIGURE 2. Meta-analysis of the effect of IVIg on disease activity scores. CI = confidence interval, IVIg = intravenous immunoglobulin.

TABLE 1. Summary of the Selected Studies on IVIg in SLE

Ref	Country	Study Design	Study Population	Outcome Measures	Findings
Lin CY, 1989	Taiwan	Prospective, observational	9 patients with lupus nephritis who did not respond to steroids and cyclophosphamide	Proteinuria	Decreased in 3 patients with Class IV lupus nephritis.
				Creatinine	Decreased in 3 patients with Class IV lupus nephritis.
				C3 and C4	Increased in 3 patients with Class IV lupus nephritis.
Maier et al, 1990	United States	Prospective observational study for 28 d	7 SLE patients with thrombocytopenia	Platelet count	5/7 patients had >50% increase in their platelet counts by day 28.
				C3 and C4	No changes (remained low).
Francioni et al, 1994	Italy	Prospective observational study for 24 mo	12 SLE patients refractory to conventional treatments	Hemoglobin	Levels increased in 11/12 patients.
				C3, C4	Levels increased in 11/12 patients.
				Platelet count	2/2 patients showed an increase.
				ESR	Progressive reduction in 11/12 patients.
				Urea	Marked improvement in all renal patients.
				Creatinine clearance	Marked improvement in all renal patients.
				Proteinuria	Marked improvement in all renal patients.
Schroeder et al, 1996	Germany	Prospective observational study for 6 wk	12 SLE patients with mildly to moderately active disease	SLAM	Declined from 7.33 (range 3–15) to 5.25 (range 0–10) ($P < 0.01$).
				AntidsDNA	Most patients showed a decline.
				ANA	No significant changes.
				C3, C4	No significant changes.
Levy et al, 1999	Israel	Prospective observational study for 1–8 mo	20 SLE patients	SLAM	Decreased from 19.3 ± 4.7 to 4 ± 2.9 ($P < 0.0001$)
				Steroid dose	Decreased from 29.7 ± 18.2 to 13.8 ± 16.7 mg/d ($P = 0.02$)
				ANA	No significant changes.
				dsDNA	No significant changes.
				Anti-SSA or anti-SSB	Significant reduction ($P = 0.04$).
				ENA	No significant changes.
				C3, C4	Significant reduction in C4 levels only ($P = 0.007$).
Boletis et al, 1999	England	Randomized controlled trial	14 patients with proliferative lupus nephritis who had received cyclophosphamide 1 g/m^2 once a month for 6 mo with daily prednisone 0.5 mg/kg	Creatinine	No substantial changes (mean change of −8 μmol/L in both groups, $P = 0.83$).
		Subjects were randomly assigned to either cyclophosphamide every 2 mo for 6 mo, and then		Creatinine clearance	No significant difference between the 2 groups (mean change of 4 mL/min in IVIg group vs 8 mL/min in cyclophosphamide group, $P = 0.80$).

		every 3 mo for 1 y (9 patients) versus IVIg 400 mg/kg monthly for 18 mo (5 patients)			
				Proteinuria	Mean change was similar in the two groups (0.23 g/d vs 0.40 g/d, $P = 0.71$).
				Cumulative prednisolone dose	Patients in the cyclophosphamide group had used marginally more prednisone than those in the IVIg group (mean cumulative dose 4719 vs 3334 mg, $P = 0.25$).
Levy et al, 2000	Israel	Pooled analysis of 7 cases treated with IVIg for 2–6 mo	7 patients with treatment-resistant membranous and membranoproliferative lupus nephritis who failed to respond to at least prednisolone and cyclophosphamide	Albumin	Plasma levels increased insignificantly from 26 ± 8 g/L to 32 ± 8 g/L.
				Total cholesterol	Decreased significantly from 339 ± 65 to 295 ± 60 mg/dL ($P = 0.009$).
				Urea	Minimal change (29 ± 10 to 29 ± 4 mg/dL).
				Creatinine	Remained static (1.6 ± 1.1 mg/dL).
				Proteinuria	Significant decrease from 5.3 ± 2.1 to 2.1 ± 1.3 g/d ($P < 0.05$).
Goodfield et al, 2004	United Kingdom	Prospective observational study for 6 mo	12 patients with histologically confirmed cutaneous SLE	Extent of skin disease (erythema, induration, scaling)	3 patients: complete clearing of skin. 5 patients: >75% improvement. 2 patients: >50% improvement. 1 patient: <50% improvement. 1 patient: nonresponder.
Monova et al, 2006	Bulgaria	Nonrandomized controlled trial Subjects were assigned to IV methylprednisolone and cyclophosphamide (48 patients), IV methylprednisolone and azathioprine (23 patients), or IVIg (61 patients)	132 patients with biopsy proven lupus nephritis	SLEDAI	Decreased from 29.2 (15–64) to 4.2 (0–8) in the IVIg group. No changes.
				C3	No changes.
				Proteinuria	Decreased from 6.4 (3.7–10.4) to 0.4 g/24h (0.0–1.3) with IVIg.
				Creatinine	Decreased from 128.7 (108–304) to 78.7 ± 78.6 μmol/L with IVIg.
				ANA	Decreased from 928 ± 786 (80–2560) to 135 ± 78 (40–640) with IVIg.
				AntidsDNA	Decreased from 735 ± 314 to 89 ± 28 with IVIg.

(*Continued*)

					The decline in the above parameters did not significantly differ across the groups.
Perricone et al, 2008	Italy	Nonrandomized controlled study	24 SLE pregnant patients with recurrent spontaneous abortions	LAI-P scale	Decreased from 0.72 ± 0.43 at the beginning of pregnancy to 0.13 ± 0.19 at the end of pregnancy ($P < 0.0001$) in the IVIg-treated group whereas the controls showed no significant changes.
		12 were treated with high-dose IVIg versus 12 were treated with prednisolone and NSAIDs (controls)			Antibodies and complement levels tended to normalize in the following number (%) of IVIg-treated patients versus controls:
				AntidsDNA	6/6 (100%) versus 3/12 (25%).
				ANA	9/12 (75%) versus 3/12 (25%).
				Anti-Ro/SSA	1/3 (33.3%) versus 2/3 (66.7%).
				Anti-La/SSB	3/3 (100%) versus 1/1 (100%).
				aCL IgM	2/2 (100%) versus 1/1 (100%).
				aCL IgG	2/4 (50%) versus 3/4 (75%).
				LAC	None improved versus 3/5 (60%).
				C4	4/5 (80%) versus 4/6 (66.7%).
				C3	5/5 (100%) versus 2/5 (40%).
				Successful pregnancies	12/12 (100%) in the IVIg-treated patients versus 9/12 (75%) among the controls.
Sherer et al, 2008	Israel	Retrospective	62 SLE patients	SLEDAI	Significant and continuous decline in the scores from 15 ± 7.8 to 5.2 ± 5.7.
				C3 and C4	Normalized in 27% of the patients.
Zandman-Goddard et al, 2012	Israel	Retrospective	11 SLE patients	SLEDAI	Significant decline in the score ($P < 0.05$).
		Monthly IVIg for 6 mo followed by therapy every 2–3 mo		Steroid dose	Significant reduction in the steroid dose by 20 mg/d ($P < 0.05$).
Camara et al, 2013	United Kingdom	Retrospective	53 SLE patients		The response to IVIg in patients with active disease and concomitant infections versus patients who were refractory to standard therapy was:
		27 SLE patients were treated with IVIg for active disease and concomitant infection		Complete remission	9/27 (33.3%) versus 6/26 (23.1%)
		26 received the IVIg as resistant to standard therapy		Partial remission	8/27 (29.6%) versus 12/26 (46.2%)
				No response	8/27 (29.6%) versus 8/26 (30.8%)

ANA = antinuclear antibody, antidsDNA = anti-double-stranded DNA, IVIg = intravenous immunoglobulin, LAI-P = Lupus Activity Index-Pregnancy, NSAIDs = nonsteroidal anti-inflammatory drugs, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

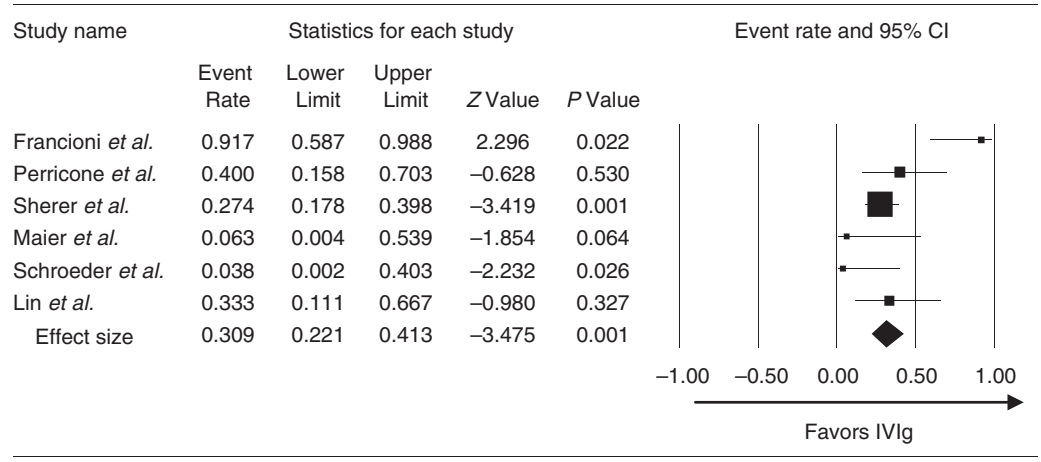

FIGURE 3. Meta-analysis of the effect of IVIg on complement levels: response rates. CI = confidence interval, IVIg = intravenous immunoglobulin.

anti-SSB autoantibodies.[8,13] Levy et al[13] found significant reduction in these autoantibodies ($P = 0.04$) but Perricone et al[8] had contradictory findings. In the latter study, the controls performed better (66.7% vs 33.3%) with regard to decline in the anti-SSA levels whereas for anti-SSB, both the treatment arms had a response rate of 100%. Pooled analysis of the autoantibodies was not performed as 2/4 studies[12,13] did not provide data on the response rate.

IVIg in Lupus Nephritis

Only 5 of the selected studies in this review included patients with lupus nephritis.[7,11,14,19,20] These studies evaluated the renal response to IVIg therapy with the following outcome measures: creatinine clearance,[7,11] creatinine,[7,14] and proteinuria.[7,11,14] All studies consistently reported a decline in proteinuria with IVIg treatment. Boletis et al[7] and Monova et al[20] found that the improvement in proteinuria was comparable between the IVIg and the cyclophosphamide-treated group. There were no substantial changes in the creatinine in 2/5 of the studies[7,14] although Francioni et al[11] demonstrated marked improvement in creatinine clearance in all 12 subjects of the study. A pooled analysis of renal outcome measures was not possible owing to the absence of details on mean values in majority (3/5) of the studies.[7,11]

DISCUSSION

This systematic review was designed to evaluate the effects of IVIg therapy in SLE. The highest strength of evidence for the cause–effect relation between treatment and outcome is derived from randomized controlled trials, but disappointingly, there is a paucity of such studies in this respect. Hence, data from uncontrolled observational studies were included in the statistical analysis as larger numbers of subjects may provide more accurate and valuable insights into the treatment effects of IVIg in SLE.

The results of this review highlights that IVIg therapy is associated with significant improvement in disease activity scores and complement levels. The vast majority (4/5) of the studies that examined the effects of IVIg on disease activity were observational. Observational studies have the tendency to overestimate treatment effects. However, across the studies there was remarkable consistency in the trend of the SLE disease activity scores, regardless of the study design.

The rationale behind employing IVIg in SLE relies on its promising results in other autoimmune diseases such as Kawasaki disease, immune thrombocytopenic purpura, autoimmune cytopenias, and antiRo/La-related congenital atrioventricular block.[13,22] IVIg interferes with the disease activity of SLE through complex processes that include various arms of the immune system, that is, Fc receptor blockade, complement regulation, and T-cell suppression.[23] IVIg preparations target cytokines including interferon γ, tumor necrosis factor α, and B-cell activating factor/APRIL (a proliferation-inducing ligand).[24] Besides, tregitopes (T-regulator cell epitopes) contained in the regions of the Fab and Fc of the IVIg induce expansion of $CD4^+$/CD25 and $FoxP3^+$ T cells.[25] As opposed to conventional immunosuppressants that predispose to systemic infections, IVIg offers the advantage of preventing infections and confers a passive immunity.[26,27]

The pooled analysis of the selected studies revealed a significant favorable response to IVIg therapy in terms of complement levels despite the inconsistencies throughout the studies. The discrepancies in the changes of the aforementioned parameter across the studies could be because of the diverse study populations, and methodological variations and the power of many of the studies was probably too low to achieve statistical significance. In clinical practice, complement levels are surrogate markers of SLE disease activity.[28,29] In vitro C3 uptake studies suggest that IVIg produces a kinetic suppression of C3 uptake and modifies the process of complement fragment deposition on erythrocytes.[30]

Based on the evidence from the small number of studies included in this review, IVIg appears to lower antidsDNA levels, the daily steroid dose requirement, and the severity of proteinuria. Although there is no robust data to support these findings, taken together these preliminary results imply that IVIg has a beneficial role as a steroid-sparing agent and maybe an alternative option in lupus nephritis. Krause et al,[31] using experimental murine models of SLE, found that IVIg had anti-idiotypic activity both to anti-DNA and anticardiolipin antibodies. IVIg infusion did not only succeed in abrogation of experimental SLE and antiphospholipid syndrome but also restored the respective antibodies to normal

levels. Moreover, the anti-idiotypic antibodies of the IVIg preparations have inhibitory effects on the spontaneous secretion of antidsDNA from blood mononuclear cells, as was demonstrated in vitro by Evans et al.[32]

FDA data shows that out of 106 patients with lupus nephritis who were treated with IVIg, a sizable proportion showed improvement in proteinuria, nephrotic syndrome, and creatinine clearance.[33] The Fc receptors (FcγRI [activating receptor for monomeric IgG], FcγRII [inhibitory immune complex receptor], and FcγRIV [activating immune complex receptors]) have been postulated to contribute to the accumulation of IgG in the kidneys in SLE. IVIg could potentially alter the balance between the inhibitory and activating Fc receptors in the kidney resulting in more degradation and urinary excretion of pathogenic autoantibodies to minimize renal parenchymal injury.[34] However, IVIg and the kidney can be regarded as a 2-edged sword, since nephrotoxicity because of renal tubular necrosis can be a serious complication of IVIg therapy.[33] A Centers for Disease Control and Prevention report cited 120 cases of nephrotoxicity worldwide with this form of therapy.[35]

There has been a paucity of well-designed controlled trials with adequate sample size on the use of IVIg in SLE. Although some of these studies reported statistically significant results, this may not necessarily be clinically meaningful. Besides, many of the studies in this review had a before–after design with limited ability to show causality. In uncontrolled studies, it is impossible to distinguish the possible effect generated by the intervention from the placebo effect or change resulting from the natural course of the disease.[36]

In conclusion, the results of this systematic review seem to suggest that IVIg is effective in reducing SLE disease activity and increasing circulating complement levels. Owing to the profound lack of studies in this area of research, it is premature and would be fallacious to make any definitive claims for or against the role of IVIg in other clinical aspects. Further research to improve the therapeutic application of IVIg in SLE is much needed and probably relies on the conception of newer generation of immunoglobulin formulations.

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