EXTENDED REPORT

IgG immunoadsorption reduces systemic lupus erythematosus activity and proteinuria: a long term observational study

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Objective: To analyse the effects of rigorous immunoglobulin removal by immunoadsorption (IAS) on proteinuria (primary outcome variable), disease activity (SIS, SLEDAI, ECLAM), and autoantibodies to double stranded DNA (anti-dsDNA) in active systemic lupus erythematosus (SLE).
Methods: 16 patients with severe SLE and renal disease, in whom cyclophosphamide was contraindicated or failed to halt disease progression, were treated with IAS for 3 months. Patients achieving at least 20% improvement in two or more of the outcome measures were considered responders and offered a 9 months' extension period.
Results: Within 3 months, 14 patients responded and 11 opted for an extension. Proteinuria decreased from 6.7 (4.6) g/day (mean (SD)) at baseline to 4.3 (3.5) g/day at 3 months and 2.9 (2.4) g/day at 12 months ($p<0.001$). From baseline to 3 and 12 months, disease activity improved independently of scoring by SIS (15 (5) to 5 (2) and to 5 (2), $p<0.0001$), SLEDAI (21 (7) to 5 (4) and to 5 (4), $p<0.0001$), or ECLAM (7 (2) to 2 (1) and to 3 (1), $p<0.0001$). Anti-dsDNA fell from 391 (647) IU/ml to 146 (218) and to 53 (50) IU/ml at 3 and 12 months, respectively. Steroids could be tapered from 117 (159) mg/day at baseline to 29 (17) mg/day at 3 months and 9 (2) mg/day at 12 months. IAS was not associated with an excess of infections. However, one patient died of septicaemia after 1 month of treatment.
Conclusion: In this negatively selected cohort of patients with SLE, IAS was associated with a significant response shown by reduced proteinuria, improved global disease activity, decreased anti-dsDNA, and lower glucocorticoid dosages, suggesting therapeutic benefit.

Autoantibodies are a hallmark of systemic lupus erythematosus (SLE), and some are pathogenic. They bind directly or through the formation of immune complexes (ICs) to cells and substrates, inducing cell activation, inflammation, and tissue damage. For example, autoantibodies against double stranded DNA (dsDNA) and Ro/SSA are typical of SLE[1] and associated with lupus glomerulonephritis,[2–7] the most common serious organ manifestation in SLE. Inhibiting the production of, or directly removing, such pathogenic autoantibodies thus should prevent their pathogenetic consequences. SLE treatment, in general, and immunosuppression, in particular, ultimately aims at interfering with autoantibody formation.

Today, intravenous pulse cyclophosphamide (IVCP) treatment is the standard treatment for severe SLE with major organ involvement.[8–11] It is effective in many, but not all, patients with lupus nephritis.[12] IVCP can cause leucopenia, is associated with a higher incidence of serious infections, malignancies, and a high risk of premature ovarian failure,[13–16] and is contraindicated in some situations, such as pregnancy.

Among other therapeutic effects, IVCP significantly reduces autoantibodies, but this effect takes time.[17] Therefore, extracorporeal treatments that directly remove antibodies have been used for patients with SLE with life threatening disease. However, plasma exchange, a vigorous non-selective approach to serum protein removal, has not been found to be generally effective in patients with SLE in prospective trials.[17 18] Moreover, when combined with IVCP, this approach may be impeded by an increase in fatal bacterial and viral infections.[19] Nevertheless, for SLE patients with life threatening disease, rapid removal of circulating ICs and autoantibodies may still provide an essential therapeutic advantage, and such immunoglobulin removal is commonly advocated for catastrophic situations.[20–23]

In contrast with plasma exchange, immunoadsorption (IAS)—or IgG apheresis—uses columns that bind human IgG. This allows for the specific and nearly complete clearance of circulating IgG and ICs, while neither removing other plasma proteins nor necessitating substitution with fresh frozen plasma or albumin.[24 25] Moreover, the plasma volume processed is not restricted, even when daily IAS is maintained.[26 27] A prospective trial with stable oral immunosuppression found that IAS not only reduces serum levels of anti-dsDNA antibodies but also improves disease activity.[28] In addition, a recent retrospective study and case reports have suggested that IAS has rapid beneficial effects in patients with SLE when applied either with additional IVCP or without any additional immunosuppressive treatment.[29–32]

Severe, potentially life threatening SLE is difficult to study in controlled clinical trials because of the heterogeneity of the disease and the concern about treatment in the comparator arm.[33] Therefore, in such patients, observational studies involving patients with nephritis as one of their major organ

Abbreviations: ACE, angiotensin converting enzyme; AT-II-Ra, angiotensin II receptor antagonist; AZA, azathioprine; dsDNA, double stranded DNA; ECLAM, European consensus league activity measurement; IAS, immunoadsorption; IC, immune complex; IVCP, intravenous cyclophosphamide; MMF, mycophenolate mofetil; SIS, SLE index score; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 1 Characteristics of the 16 patients with SLE at the start of IAS treatment

Characteristics	
Age (years), mean (SD)	30 (11)
Female, No (%)	14 (88)
White, No (%)	14 (88)
East Asian, No (%)	2 (13)
Disease duration (years), mean (SD)	6.4 (8.1)
SIS, mean (SD)	15 (6)
Major organ involvement, No (%)	
Cerebral	6 (38)
Lung	7 (44)
Renal	16 (100)
Renal biopsy, No (%)	14 (88)
GN WHO II	1
GN WHO III	1
GN WHO IV	10
GN WHO V	2
Indication for IAS, No (%)	
Disease progression despite IVCP	9 (56)
IVCP contraindicated or denied	7 (44)

GN, glomerulonephritis; IVCP, intravenous pulse cyclophosphamide.

manifestations have often been used as a prelude to controlled trials. To this end, the present observational study evaluates the short and long term efficacy of IAS in patients with lupus nephritis.

PATIENTS AND METHODS

Study design

In this long term observational study,[33–35] all data were prospectively collected according to predefined IAS protocols, standardised laboratory analyses, and established routine clinical care to obtain unbiased and complete information. We included patients with highly active SLE and evidence of lupus nephritis if previous standard IVCP treatment had not led to a reduction of global disease activity of at least 20% or was contraindicated.

Improvement in proteinuria was defined as the primary end point, as it is the main feature of renal disease and regarded as the most objective system to study.[33] Reductions in global disease activity measured by the SLE index score (SIS) and in anti-dsDNA were defined as secondary end points. A reduction of the pretreatment values of these measures by 50% or more was considered a major response (R50), a decrease ⩾20% was considered a minor response (R20).

Patients who showed at least an R20 in at least two of the outcome measures were regarded as responders. After 3 months of IAS treatment, efficacy was assessed and responders were offered a 9 month extension and reanalysed 6 and 12 months after the start of IAS treatment. If IAS was stopped earlier, the last observation under IAS was carried forward.

SLE disease activity and organ damage

As recommended for a long term observational study, we have collected global information on SLE activity as integrated in the SIS, SLE Disease Activity Index (SLEDAI), and the European consensus league activity measurement (ECLAM) scores,[33 36–38] which are highly correlated,[33 34 39 40] as well as data on disease related damage (as indicated by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR)[41]), adverse events, infections, flares, and concomitant immunomodulating drug treatment.[33–35] Severe SLE flares were defined as those requiring admission to hospital and/or IVCP treatment, and minor flares as those requiring doubling of the daily corticosteroid dosage.

Patients

Sixteen patients with severe SLE and lupus nephritis underwent IAS treatment. Table 1 shows the patients' baseline characteristics. All patients fulfilled the ACR criteria for SLE,[42] had highly active SLE as indicated by an SIS ⩾12 and evidence of lupus nephritis as indicated by a nephritic urinary sediment (cellular casts) and proteinuria ⩾0.5 g/day. Lupus nephritis was confirmed by renal biopsy in all but two patients.

Immunoadsorption (IAS)

Ig Therasorb columns (Miltenyi Biotec, Bergisch Gladbach, Germany) are CE registered in Europe (DAR 9801) for the treatment of autoimmune diseases. IAS is employed, based on uncontrolled evidence, [28 31 43] as a compassionate treatment approach in selected patients at our tertiary care centre. All patients gave informed consent both to this experimental treatment and to the anonymous analysis of data obtained in the course of clinical care.

IAS was performed as described,[29 44–49] using columns with polyclonal sheep antibodies to human immunoglobulins. In a single treatment session, a total plasma volume of 6000–8000 ml was processed. The IAS frequency was gradually reduced with clinical improvement from 3.2 (0.8) sessions/week (mean (SD)) to two consecutive treatment sessions within 3 days (one cycle) every 3 weeks (0.9 (0.2) sessions/week) in month 12.

Additional immunosuppressive treatment

Patients receiving IVCP at the start of IAS treatment were changed to azathioprine (AZA) or mycophenolate mofetil (MMF)[50] when clinical improvement was seen. For patients receiving oral immunosuppressive drugs before IAS treatment, the drug and dosage were kept constant.

Assessment and laboratory studies

All patients were followed up prospectively at one centre and assessed before each IAS session. Every time the patients' recent history was taken, a clinical examination was performed and blood samples were drawn. Complete blood count, erythrocyte sedimentation rate, serum albumin, C reactive protein, glucose, creatinine, blood urea nitrogen, urine analysis by dipstick, urinary sediment, 24 hour proteinuria as well as anti-dsDNA antibodies (radioimmunoassay), C3c and C4 (enzyme linked immunosorbent assay (ELISA)) were determined according to standard laboratory procedures.

Statistical analysis

All group results were expressed as the mean (SD). A paired Student's *t* test, Student's *t* test, and Fisher's exact test (two tailed) were used for comparison of individual paired values, group values, and discriminatory measures. One way analysis of variance was used for repeated measurements of the same variable, where appropriate. Wilcoxon's matched pairs test was used for the comparison of individual paired values if the distribution was not Gaussian.

RESULTS

Primary end point: decreasing proteinuria within 3 months of treatment

Proteinuria had consistently increased to a mean of 5.0 (4.0) g/day 1 month before IAS and to a maximum of 6.4 (4.0) g/day when IAS treatment was finally started (baseline). After IAS was begun, proteinuria decreased to 4.5 (4.6) g/day within 3 months ($p = 0.03$), while serum albumin and creatinine clearance tended to increase. Fifty six per cent of patients reached an R50 and an additional 13% at least an R20 in proteinuria (table 2), while the percentage of patients with nephritic range proteinuria (⩾3.5 g/24 h)

Table 2 Renal and global SLE activity before and after 3 months of IAS

	At start of IAS (n = 16)	3 Months IAS (n = 16)	p Value
Renal function			
Proteinuria (g/day)	6.4 (4.0)	4.5 (4.6)	0.03
R20/R50 (%)		69/56	
Serum albumin (g/l)	28.5 (8.0)	29.5 (7.0)	NS
Creatinine clearance (ml/min)	54 (32)	78 (48)	0.02
Serum creatinine (μmol/l)	155 (95)	140 (105)	NS
SLE activity			
SIS	17 (6)	6 (3)	<0.0001
R20/R50 (%)		94/81	
SLEDAI	21 (6)	6 (4)	<0.0001
ECLAM	8 (3)	3 (2)	<0.0001
Anti-dsDNA (IU/ml)	460 (760)	107 (190)	<0.002
R20/R50 (%)		81/75	
C3c (g/l)	0.4 (0.2)	0.7 (0.3)	<0.01
C4 (g/l)	0.1 (0.05)	0.2 (0.09)	<0.01

Normal ranges: albumin 34–48 g/l; C3c 0.9–1.8 g/l; C4 0.1–0.4 g/l; creatinine 0–110 μmol/l; creatinine clearance 80–120 ml/min; proteinuria 0–0.18 g/day.
Results are shown as mean (SD) unless stated otherwise.

decreased from 63% to 44%. In 31% of the patients, proteinuria decreased below 0.5 g/24 h after 3 months of IAS, although all patients had proteinuria >0.5 g/24 h at the start of treatment.

Secondary end points: global disease activity and anti-dsDNA

Disease activity had increased to an SIS of 14 (3) one month before IAS and further increased to 17 (6) at baseline. Rapid improvement was observed within 2 weeks, indicated by a decrease in SIS to 8 (2) ($p<0.0001$), and subsequently to 6 (3) by the 3 month end point ($p<0.0001$). Eighty one per cent of the patients achieved an R50 and 94% at least an R20 in disease activity measured by SIS. Similar significant results were obtained with SLEDAI and ECLAM[51] (table 2).

Anti-dsDNA levels had increased to 455 (630) IU/ml one month before IAS was started. From 460 (760) IU/ml at baseline, anti-dsDNA serum levels decreased to 107 (190) IU/ml ($p<0.002$) after 3 months of IAS. For anti-dsDNA autoantibodies, 75% of the patients reached an R50, and an additional 6% at least an R20. Concomitantly, complement factors C3c and C4 increased (table 2).

Responders and non-responders at 3 months

After 3 months of observation, 14 patients (88%) met response criteria and were offered an additional 9 months of IAS treatment (''extended IAS''), to which 11 patients consented.

The remaining two patients who had started IAS treatment were not eligible. One patient died of *Pseudomonas septicaemia* after 1 month of treatment.[29] Another patient with a history of bladder carcinoma (curatively resected) due to previous IVCP treatment did not show an adequate response to IAS and was subsequently included in another protocol.[52]

Of the three eligible patients who did not consent to continuing IAS treatment despite a significant response, one patient's disease is currently well controlled with low dose corticoids after giving birth to a healthy child; one patient

Table 3 Renal disease, SLE activity, and damage scores under extended IAS

	Start of IAS (n = 11)	3 mo IAS (n = 11)	6 mo IAS (n = 11)	12 mo IAS (n = 11)	p Value
Renal function					
Proteinuria (g/day)	6.7 (4.6)	4.3 (3.5)	2.5 (2.5)	2.9 (2.4)	<0.001
R20/R50 (%)	–	55/45	91/64	82/64	
Serum albumin (g/l)	26.3 (5.8)	29.5 (6.0)	33.2 (7.1)	35.0 (8.3)	<0.0001
Creatinine clearance (ml/min)	58.6 (33.8)	76.5 (46.1)	74.5 (28.3)	67.0 (33.0)	NS
Serum creatinine (μmol/l)	145 (75)	120 (50)	120 (35)	125 (60)	NS
SLE activity					
SIS	15 (5)	5 (2)	4 (1)	5 (2)	<0.0001
R20/R50 (%)	-	100/82	100/91	100/73	
SLEDAI	21 (7)	5 (4)	4 (3)	5 (4)	<0.0001
ECLAM	7 (2)	2 (1)	2 (1)	3 (1)	<0.0001
Anti-dsDNA (IU/ml)	391 (647)	146 (218)	77 (78)	53 (50)	0.0002
R20/R50 (%)	-	82/82	91/64	91/64	
C3c (g/l)	0.5 (0.1)	0.8 (0.2)	0.9 (0.1)	0.8 (0.2)	<0.002
C4 (g/l)	0.1 (0.05)	0.2 (0.09)	0.2 (0.06)	0.2 (0.06)	<0.0001
SLE damage (SLICC/ACR)	1.3 (0.8)		1.3 (0.9)	1.2 (1.0)	NS
IAS frequency (sessions/week)	–	1.3 (0.4)	1.0 (0.2)	0.9 (0.2)	

Normal ranges are provided in table 2. Data are analysed by one way analysis of variance.
Results are shown as mean (SD) unless stated otherwise.

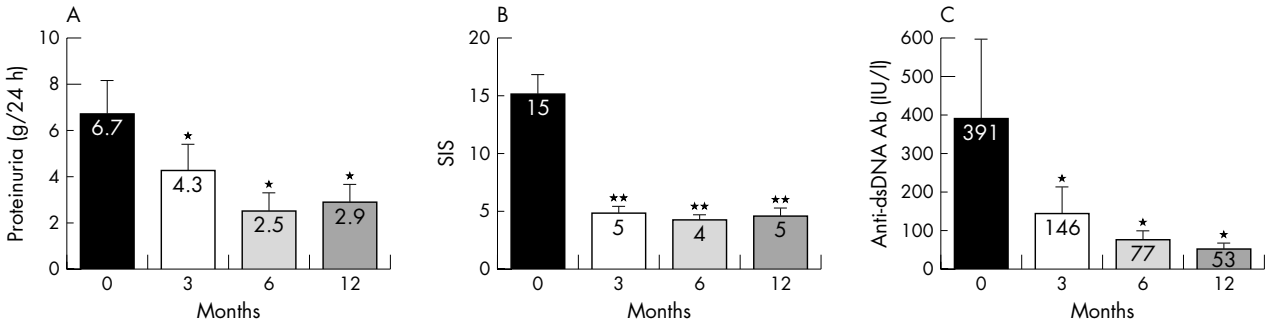

Figure 1 Reduction of (A) proteinuria; (B) overall disease activity; and (C) pretreatment anti-dsDNA levels in patients undergoing extended IAS. In patients who were offered an extension of IAS, a significant reduction in all primary and secondary outcome parameters was achieved within 3 months of IAS and a further reduction occurred after 12 months of treatment. Data are shown at the start of IAS and after 3, 6, and 12 months of treatment. *p<0.05; **p<0.001.

experienced a severe flare of pneumonitis 14 months after IAS treatment was stopped and finally underwent autologous stem cell transplantation, and, finally, one Asian patient returned to her home country and was lost to further follow up. Thus, a total of 11 patients entered the trial extension.

Primary end point: stable improvement in proteinuria during extended IAS

All 11 patients who opted for an extension of IAS had achieved a significant reduction in proteinuria (from 6.7 (4.6) to 4.3 (3.5) g/day, p<0.05) within 3 months of treatment. During extended IAS, proteinuria was further reduced to 2.9 (2.4) g/day by 12 months from baseline (p<0.001, fig 1A, table 3). The decrease in proteinuria was associated with an increase in serum albumin and a stabilisation of serum creatinine and creatinine clearance (table 3).

After 12 months of treatment, 64% of the patients had reached an R50 and an additional 18% at least an R20 in proteinuria (table 3). Two patients did not respond: One experienced a major nephritic flare after 10 months of IAS, which was stopped thereafter. The other patient showed stable proteinuria (1.12 g/day at baseline and 0.97 g/day at the end of IAS).

Secondary end point: low stable disease activity and reduced anti-dsDNA during extended IAS

Disease activity measured by SIS had decreased from 15 (5) at baseline to 5 (2) after 3 months. Extended IAS stabilised this low to moderate disease activity at 5 (2) after 12 months (p<0.0001, fig 1B, table 3). All patients showed at least an R20 in SIS, and 73% even an R50. SLEDAI and ECLAM score results were similar; the SLICC/ACR was stable (table 3).

Pretreatment anti-dsDNA serum levels decreased from 391 (647) IU/l to 146 (218) IU/l within 3 months and further to 53 (50) IU/l after 12 months of treatment (p = 0.0002 *v* baseline, fig 1C, table 3). For anti-dsDNA, 64% of the patients reached an R50 and an additional 27% at least an R20. In parallel, C3c and C4 increased (fig 1C, table 3).

Intention to treat analysis, last observation carried forward

The above analyses were performed for the 11 patients who continued IAS. However, even when analysing all 16 patients and regarding those who had dropped out for any reason as a failure of treatment, 56% reached an R20 in proteinuria (and 44% an R50), 69% an R20 in SIS (50% an R50), and 63% an R20 in anti-dsDNA (50% an R50).

Table 4 Concomitant immunosuppressive and immunomodulatory treatment

Glucocorticoids	No of patients (%)	Dose/day (mg), mean (SD)					
⩽14 days before IAS	16 (100)	80 (84)					
Start of IAS	16 (100)	117 (159)					
After 3 months	16 (100)	29 (17)*					
After 6 months	11 (100)	19 (13)*					
After 12 months	11 (100)	9 (2)*					
IVCP	**No of patients (%)**	**Pulses**	**Cumulative dose (mg), mean (SD)**				
12–13 Months before IAS	9 (56)	7 (5)	5493 (4055)				
±3 Months from start of IAS	9 (56)	3 (1)	5503 (3923)				
3–6 Months after start of IAS	1 (9)	1	700				
6–12 Months after start of IAS	0 (0)	0	0				
	Oral immunomodulation with:						
Time	**AZA†**	**CQ†**	**CP†**	**MMF†**	**MTX†**	**None†**	
⩽1 Year before IAS	2 (13)	3 (19)‡	2 (13)	0 (0)	2 (13)	8 (50)	
⩽3 Months before IAS	2 (13)	1 (6)	4 (25)	0 (0)	1 (6)	8 (50)	
Start of IAS	2 (13)	2 (13)‡	4 (25)	0 (0)	1 (6)	8 (50)	
After 3 months	3 (19)	4 (25)	4 (25)	1 (6)	1 (6)	5 (31)	
After 6 months	2 (18)	3 (27)§	2 (18)	4 (36)	0 (0)	2 (18)	
After 12 months	2 (18)	3 (27)§	1 (9)	5 (45)	0 (0)	2 (18)	

AZA, azathioprine; CQ, chloroquine; CP, cyclophosphamide by mouth; MMF, mycophenolate mofetil; MTX, methotrexate; IVCP, intravenous cyclophosphamide.
*Indicates a p<0.05; dosage of oral immunomodulation: AZA 100 mg/day, CQ 250 mg/day, MTX 25 mg/week, CP 100 mg/day, MMF 2 g/day; †No (%) of patients; chloroquine was used as monotherapy or as an adjunct (in ‡one patient before, ‡one patient at the start of IAS, and in §two patients during IAS).

Table 5 Infections and flares occurring during IAS treatment

	3 Months IAS (severe/minor)	Extended IAS (severe/minor)
Infections		
Fatal septicaemia	1/0	0/0
Respiratory	0/1	0/0
Gastrointestinal	1/0	0/0
Urinary tract	0/0	2/1
Local bacterial	0/1	0/0
Herpes zoster	0/0	0/1
Other viral	0/0	0/0
More than one infection	0/0	0/0
Flares	2/2	2/1

Severe infections were defined as those requiring admission to hospital and/or IV antibiotics; minor infections as those requiring oral antibiotics. We defined a severe flare as those requiring admission to hospital and/or IVCP and a minor flare requiring doubling of glucocorticoids.

Kinetics of anti-dsDNA autoantibodies and immunoglobulin

During the first cycle of IAS (that is, two sessions within 3 days), anti-dsDNA antibody levels fell from 349 (726) IU/ml (mean (SD)) to 86 (249) IU/ml. The average complete cycle reduced anti-dsDNA by 85% in the first 3 months of IAS and by 93% during extended IAS. Autoantibody levels after resynthesis in the treatment-free interval never exceeded the pretreatment concentrations of the previous cycle.

The first cycle of IAS removed IgG below the lower limit of detection (<1.95 g/l) in 75% of the patients, reducing mean serum IgG from 9.72 (3.71) g/l to 2.11 (0.44) g/l. The average cycle achieved IgG reduction below the lower limit of detection in 88% of the patients during the first 3 months of IAS treatment and in 93% during extended IAS.

Glucocorticoids, immunosuppression, and additional drug treatment

All patients received glucocorticoids with increasing dosage before and decreasing dosage during IAS (table 4).

Glucocorticoid dosage could be reduced, IVCP was switched to less aggressive oral immunomodulatory treatment (AZA or MMF, respectively) or to oral glucocorticoids only. One additional patient who had had IVCP more than 3 months before IAS and oral cyclophosphamide at the start of IAS could also be switched to MMF, as could one patient who no longer tolerated oral MTX. In five patients, oral immunomodulators were kept constant, and two patients never received immunomodulatory drugs in combination with IAS.

Twelve (75%) of the 16 IAS treated patients with SLE had undergone IVCP in the course of their disease.[9] Nine (56%) patients were given IVCP within 3 months before the start of and/or concomitantly with IAS (mean (SD) 1.5 (1.1) months between the last bolus of IVCP and the start of IAS). With clinical improvement, all patients were switched to oral immunomodulatory treatment (AZA or MMF, respectively) or glucocorticoids only. Five patients were already receiving oral immunomodulation, which was continued. Two patients did not receive any immunomodulatory drugs in combination with IAS, because of contraindications or because they refused (table 4). Although MMF may be more potent than AZA in its effect on proteinuria, we did not see any difference in outcome (proteinuria R50 3/5 (60%) and 2/3 (67%) for MMF and AZA treated patients, respectively).

Sixty nine per cent of patients were given angiotensin converting enzyme (ACE) inhibitors (ACE-I) or angiotensin II receptor antagonists (AT-II-Ra) before the start of IAS (mean (SD) 6.7 (8.6) months); drug and dosage were kept constant. Although a reduction in proteinuria might be expected within this period,[53] proteinuria steadily increased before the start of IAS. Four patients did not tolerate or consent to this treatment. After 3 months of treatment, proteinuria decreased in both ACE-I/AT-II-Ra treated (58% R20) and untreated (66% R20) patients.

Flares during IAS treatment

Four patients experienced at least one flare during IAS. Two severe flares and two minor flares were seen within the first 3 months: One patient was admitted because of a severe nephritic flare and given intravenous glucocorticoids twice for minor flares. In this patient, IAS was stopped after 3 months because of an insufficient response. Another patient was admitted after 2 weeks of IAS because of a relapse of her cerebral SLE and successfully treated with high dose glucocorticoids.

During the extension period, two severe flares and 1 minor flare occurred: one patient was admitted with venous thrombosis. After a second admission with a massive renal flare, IAS was stopped and IVCP restarted. One additional patient received high dose IV steroid treatment because of a cutaneous SLE flare after intensive exposure to ultraviolet light.

Infections and side effects

Eight infections occurred in the 16 IAS treated patients with SLE: we observed a total of four episodes of severe infections in two patients (table 5). One patient died of *Pseudomonas septicaemia* after 1 month of combination treatment with IVCP and IAS.[29]

Three anaphylactic episodes were seen, two of them associated with newly started IV drug treatment (IV iron compounds and ranitidine, respectively), and one single episode of orthostatic dysregulation (fainting) occurred (in a total of 708 IAS sessions). All patients receiving extended IAS treatment required erythropoietin at least once.

DISCUSSION

Extracorporeal treatments are a recommended rescue strategy in severely ill patients with SLE when conventional strategies fail or are contraindicated.[20] Because IAS is expensive and still experimental in SLE, patients finally undergoing IAS are negatively selected and characterised by active and progressive SLE despite conventional treatment, including IVCP. Thus, interpreting therapeutic effects in these patients with heterogeneous manifestations of lupus against a background of previous immunosuppressive treatment is difficult. To cope with these limitations, we observed most of the patients for a whole year and concentrated on proteinuria as the main feature of renal disease, which is regarded as the most objective system to study in SLE.[33] In addition, important information relates to general disease activity, damage, and the reduction of anti-dsDNA antibodies, because decreased serum levels of these pathogenic antibodies after treatment reflect the effectiveness of IAS on antibody removal, and decreased levels before treatment provide a surrogate biological marker for effects on disease activity. Despite all the inherent limitations, the results suggest that IAS has a therapeutic effect for most patients treated in our centre.

In extracorporeal treatments, the plasma volume processed for each session and the total number and frequency of sessions influence the outcome.[54] Therefore, a low rate of plasma removal and IAS sessions might have interfered with outcome in some previous reports on other extracorporeal procedures like plasma exchange.[17 55 56] In contrast, our treatment protocol demanded that 6000 to 8000 ml plasma

were processed in a single session, an amount consistently shown to remove more immunoglobulin than is being produced in the variable interval between two cycles. Accordingly, IAS decreased anti-dsDNA autoantibodies significantly, rapidly, and constantly throughout 1 year of treatment, and autoantibody removal capacity exceeded the production of autoantibodies in the treatment-free interval. As anti-dsDNA decreased, serum complement levels increased, suggesting reduced IC formation. This was also mirrored in a significant decrease in global disease activity, which was independent of the score used.[51] Because all these disease indices contain information on autoantibodies and/or serum complement levels, one can conclude that the marked short term effects on disease activity are brought about by sufficient removal of pathogenic autoantibodies and ICs.

On the other hand, IAS significantly decreased proteinuria after 3 months of treatment, which cannot be directly attributed to the rapid immunoglobulin and IC removal, but probably represents a consecutive treatment benefit. In line with these findings, additional renal damage was prevented, as demonstrated by stable SLICC/ACR scores. Consequently, glucocorticoid intake could be reduced and IVCP could be changed to less aggressive oral treatment (AZA and MMF, respectively). This change by itself, and MMF in particular, may have positively influenced the course of disease, but we found no differences between AZA and MMF treated patients, and lupus activity and renal function also improved in those patients who did not receive any additional immunomodulation. However, it is difficult to exclude conclusively a carryover effect of previous treatments—for example, cyclophosphamide. Nevertheless, we observed a steady increase in proteinuria and disease activity before IAS despite IVCP or ACE-I-/AT-II-RA treatment, but a decrease during IAS also in those patients without these additional drugs, suggesting that IAS indeed exerted beneficial effects in our patients.

Despite all the methodological limitations, our observations suggest that IAS has therapeutic effects in patients with severe SLE. All three predefined outcome variables (proteinuria, disease activity, and anti-dsDNA levels) improved within 3 months of treatment and improved further or at least stabilised thereafter, while patients receiving IAS did not appear to be more prone to adverse events and infections than expected given their rather high disease activity.[57] Prospective controlled trials are warranted to determine conclusively the role of IAS in SLE treatment.

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