Immunoadsorption (IAS) as a rescue therapy in SLE: considerations on safety and efficacy

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Summary. Objective. In SLE, extracorporeal procedures aiming at reduction of immunoglobulin (Ig) and immune complexes (IC) are used as a rescue therapy. Plasma exchange (PE) has not been proven overall effective in SLE, and long-term treatment in particular has been associated with severe bacterial and viral infections. Immunoadsorption (IAS), in contrast, selectively removes Ig and IC and may thus be safer. We therefore investigated the rate of infections in SLE patients who were undergoing long-term IAS.

Methods. 16 SLE patients were treated with ≥10 courses of IAS, and nine patients with highly active disease received pulse cyclophosphamide (IVCP) therapy in parallel. We retrospectively analysed the records of all these patients for the occurrence of infections. Patients receiving IAS therapy plus IVCP were compared with 25 patients with similarly active disease treated with standard IVCP therapy within the same observation period. Patients receiving IAS without additional IVCP were compared with patients with similarly moderate disease activity receiving neither IAS nor IVCP.

Results. No potentially life-threatening viral infection occurred in IAS-treated patients and episodes of herpes zoster were equally distributed. No severe infection was observed during IAS without concomitant cyclophosphamide. As expected, more patients with highly active disease receiving IVCP experienced infections than those with less active disease (16 of 34 [47%] vs. 2 of 22 [9%], p<0.04). On comparing the two groups with highly active disease, infections were similar (IAS+IVCP: 3 of 9 patients [33%], IVCP only: 5 of 25 [20%]), but one patient receiving IAS+IVCP died of septicaemia. Disease activity significantly decreased in both groups treated with IAS.

Conclusion. IAS has an acceptable safety profile with regard to severe infections and appears safe with regard to severe viral disease. Highly active disease and IVCP therapy increase the risk of severe infections in SLE.

Key words: Infection, immunoadsorption (IgG apheresis), SLE.

The pathophysiological and clinical manifestations of systemic lupus erythematosus (SLE) are mediated by a variety of autoantibodies, either directly or via the formation of soluble immune complexes (IC) [1]. SLE therapy, particularly immunosuppression, mainly aims at interfering with autoantibody formation, but methods of direct antibody removal may also be of benefit. Plasma exchange (PE), a crude approach to immunoglobulin (Ig) removal, has not been found generally effective in prospective trials [2, 3]. Moreover, when combined with intravenous pulse cyclophosphamide (IVCP), this approach led to an increase in fatal bacterial and viral infections [4]. However, for SLE patients with life threatening disease, rapid removal of circulating IC and autoantibodies may still provide an essential therapeutic advantage, and such Ig removal is commonly advocated for catastrophic situations [5].

In contrast to PE, immunoadsorption (IAS, also called IgG apheresis) using affinity columns that bind human IgG achieves specific and nearly complete clearance of circulating IgG, while not removing other plasma proteins or necessitating concomitant substitution with fresh-frozen plasma or albumin solutions [6, 7]. In addition, the plasma volume processed is not limited, even when patients are maintained on daily IAS [8, 9], and IAS does not lead to increased antibody re-synthesis [10]. Unfortunately, IAS has never been prospectively tried against a control group not receiving adsorption therapy. However, there is some preliminary evidence for its efficacy: in a prospective randomised trial of two immunoadsorbents in SLE patients under stable oral immunosuppressants, IAS appeared to significantly reduce disease activity and serum levels of anti-dsDNA antibodies [11]. In addition, case reports have suggested beneficial effects of IAS in SLE patients even when used without additional immunosuppressive therapy [12].

So far, IAS has appeared to be a fairly safe procedure in clinical practice [13], and most patients are in fact being treated with long-term IAS therapy. However, it was long-term PE combined with cyclophosphamide that was associated with fatal infections in SLE [4], where infections in general are important complications and a leading cause of death [14-16]. Despite this potential risk, no systematic attempts have been made to study the rate of severe infections in SLE patients receiving long-term IAS therapy [14]. Therefore, and in view of negative experience with
PE in combination with pulse cyclophosphamide therapy (IVCP) [4], we have retrospectively analysed the safety of IAS in patients with active SLE.

**Patients and methods**

**Study design**

We performed this investigation as a retrospective long-term observational study. All data on infections and mortality were derived from the patients’ charts to obtain unbiased and complete information according to established routine clinical care.

**Patients**

We included all SLE patients who had undergone long-term IAS treatment (10 cycles or more) in our units and identified 16 such patients. To exclude any selection bias when forming control groups, we analysed the charts of all SLE patients who had been assessed within a defined interval before the end of observation (spanning from January 1998 to the end of November 2000, with an observation time of up to 35 months). As detailed below, we compared two patient groups with highly active disease receiving IVCP with or without concomitant IAS. In addition, we compared a group with moderately active disease without IVCP therapy with a similar group receiving IAS without IVCP. All patients were followed exclusively at one centre and assessed on a regular basis. At each visit the patient history was taken, a clinical examination was performed and blood samples were drawn for standardised laboratory tests.

**Patients receiving IAS**

Ig Therasorb® columns are CE-registered in Europe (DAR 9801) for the treatment of autoimmune diseases. Based on positive experience in uncontrolled clinical trials and case studies [11, 12, 17], IAS is used in our tertiary care centre as compassionate-care treatment in selected SLE patients, on condition of informed consent.

We identified all patients receiving IAS treatment for their SLE. Out of 18 patients, IAS was stopped in two at the patients’ request after 5 and 7 sessions, respectively. In neither of these cases were infections the reason for ceasing IAS therapy. The other patients underwent long-term IAS treatment, defined as a minimum of 10 sessions (n = 16, m/f 14/2, Caucasian/Asian 14/2, mean number of sessions 65 ± 49, mean duration of IAS therapy 23 ± 21 months (95% confidence interval 12–35 months). Nine of these patients had highly active disease (as detailed below) and received additional IVCP (IAS + IVCP = group A, mean observation time 19 ± 18 months). The remaining seven patients had moderately active disease and were treated with IAS alone or in combination with different oral immunomodulators excluding IVCP (IAS only = group B, mean observation time 29 ± 25 months).

SLE patients were offered IAS therapy for catastrophic antiphospholipid antibody syndrome (APLAS) (n = 1) in addition to cyclophosphamide therapy when IVCP alone had not sufficiently controlled their disease activity (n = 9), or had failed to halt disease progression or had been contraindicated (n = 6) (Table 1). All patients gave informed consent both to this experimental treatment and to the anonymous analysis of data obtained in the course of clinical care.

<table>
<thead>
<tr>
<th>Age, sex</th>
<th>SIS</th>
<th>Involved organs</th>
<th>Indication for IAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IAS + IVCP</td>
<td>20 f</td>
<td>25</td>
<td>CNS, R, S, J, BM</td>
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<td></td>
<td>14 f</td>
<td>18</td>
<td>P, R</td>
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<td>23 f</td>
<td>18</td>
<td>CNS, R</td>
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<td></td>
<td>36 f</td>
<td>18</td>
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<td></td>
<td>17 f</td>
<td>18</td>
<td>CNS, R, S</td>
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<tr>
<td></td>
<td>41 m</td>
<td>16</td>
<td>R, CNS, BM</td>
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<tr>
<td></td>
<td>45 f</td>
<td>13</td>
<td>R, P, BM</td>
</tr>
<tr>
<td></td>
<td>40 m</td>
<td>12</td>
<td>CNS, APLAS</td>
</tr>
<tr>
<td></td>
<td>25 f</td>
<td>8</td>
<td>R, P, M</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IAS only</td>
<td>19 f</td>
<td>12</td>
<td>APLAS</td>
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<tr>
<td></td>
<td>23 f</td>
<td>12</td>
<td>R</td>
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<tr>
<td></td>
<td>38 f</td>
<td>12</td>
<td>CNS, R, P, M, S</td>
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<tr>
<td></td>
<td>39 f</td>
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<td></td>
<td>27 f</td>
<td>7</td>
<td>BM, J</td>
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<tr>
<td></td>
<td>28 f</td>
<td>7</td>
<td>R, P, APLAS</td>
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<td></td>
<td>37 f</td>
<td>6</td>
<td>R</td>
</tr>
</tbody>
</table>

*Involved organs: BM bone marrow, CNS central nervous system, J Joints, M myocardial, P pulmonary, R renal, S serositis. CP cyclophosphamide; IAS immunoadsorption; IVCP intravenous pulse cyclophosphamide; m male; f female; APLAS antiphospholipid-antibody syndrome. 14 patients were of Caucasian, 2 of Asian origin (indicated by b).*
Control groups

We analysed the charts of all SLE patients who were seen at our unit (both inpatient and outpatient departments) during the observation period. Since the risk of infection in SLE has been reported to correlate with disease activity [18–22] and cyclophosphamide treatment [18, 23], we compared patients treated with IAS with two control groups closely matched in these respects. The first control group consisted of all consecutive patients who had highly active disease and were treated with IVCP pulse therapy only (IVCP only = group C, n = 25, mean observation time 21±9 months); the second group was formed by all remaining patients who received neither IAS nor IVCP and who had at least moderately active disease indicated by a SIS > 4 and at least one hospital admission (group D, n = 15, mean observation time 19±10 months).

Disease activity assessment and laboratory studies

Patients were assessed on a regular basis depending on their clinical state. Complete blood counts, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), creatinine, blood urea nitrogen (BUN), and urine were analysed using standard laboratory procedures. Anti-dsDNA antibodies, and serum levels of C3c and C4 were also determined. Disease activity was assessed using the SLE activity-index score (SIS), an NIH-derived activity index that has been validated and correlates well with all other major SLE activity scores such as SLEDAI, SLAM, ECLAM or BILAG [24–26]. A SIS of 4 or lower is characteristic of inactive disease, a SIS > 4 and ≤12 indicates moderate activity, and a SIS higher than 12 suggests very active disease.

Comparison of patients with and without immunoadsorption

We compared two groups with highly active disease (A and C, i.e. IAS + IVCP and IVCP only) and two with moderate-ly active disease (B and D, i.e. IAS or not and no IVCP). Among the four groups there were no significant differences in sex distribution, mean age, disease duration, or the mean observation period (Table 2). Disease activity as measured by the SIS score matched within the groups with highly active (16±5 vs. 16±5) and moderately active (9±3 vs. 9±3) disease (Table 2).

As also shown in Table 2, the proportions of patients with renal, CNS and interstitial pulmonary involvement were similar in the two groups with highly active, IVCP-treated disease. As expected, organ manifestations were less prominent in the groups with moderately active disease, although renal involvement was common in group B (71%), particularly when compared with group D (20%, p<0.02).

Immunoadsorption (IAS) procedure

Blood was drawn via a 15-gauge needle from a peripheral vein at a flow rate of 50–80 ml/ min. The blood was anticoagulated with a continuous infusion of citrate (ACD-A, anticoagulant citrate dextrose, formula A; Baxter, Munich, Germany), at a volume ratio of 1:22, and sodium heparin (1000–1500 IE/h, Heparin, Baxter, Vienna, Austria). Plasma was separated from blood cells with the Autothersis-C therapeucic plasma system (TIPS; Baxter, Germany) and transferred into an Adsorption-Desorption Automate system (ADA system, Medicap, Ulrichstein, Germany) at a flow rate of 28–38 ml/min. This system consists of two columns each containing 150 ml of sepharose coupled with polyclonal sheep antibodies to human Ig (Ig-Therasorb, Miltenyi, Bergisch Gladbach, Germany). 400–500 ml of plasma are alternately loaded onto one column while the other column is regenerated. Columns were regenerated by protein elution with glycine buffer at pH 2.8, followed by washing cycles with phosphate-buffered saline and isotonic sodium chloride solution. In a single treatment session, 14–20 rounds were performed, resulting in a total processed plasma volume of 5600–8000 ml in 3.5–4.0 h. After passing through the column, the plasma was mixed with the separated blood cells and

Table 2. Characteristics of all patient groups at the beginning of observation. Comparison of two IVCP-treated groups with highly active disease with or without IAS (i.e. groups A and C, respectively, left) and two groups with moderately active disease with or without IAS (i.e. groups B and D, respectively, right) a

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group C</th>
<th>Group B</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IAS + IVCP</td>
<td>IVCP only</td>
<td>IAS only</td>
<td>Controls</td>
</tr>
<tr>
<td>SIS mean±SD</td>
<td>16±5</td>
<td>16±5</td>
<td>9±3</td>
<td>9±3</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>7 (78)</td>
<td>22 (88)</td>
<td>6 (86)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Age, mean±SD years</td>
<td>29.0±11.6</td>
<td>31.0±9.4</td>
<td>30.1±7.9</td>
<td>36.3±13.9</td>
</tr>
<tr>
<td>Disease duration, mean±SD months</td>
<td>29±47</td>
<td>53±71</td>
<td>83±96</td>
<td>54±79</td>
</tr>
<tr>
<td>Major organ involvement, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebral</td>
<td>6 (67)</td>
<td>14 (56)</td>
<td>1 (14)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>5 (56)</td>
<td>5 (20)</td>
<td>2 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal</td>
<td>8 (89)</td>
<td>20 (80)</td>
<td>5 (71)*</td>
<td>3 (20)*</td>
</tr>
<tr>
<td>Renal biopsy, no. (%)</td>
<td>7 (78)</td>
<td>14 (56)</td>
<td>5 (71)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>GN WHO II</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (14)</td>
<td>1 (7)</td>
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<tr>
<td>GN WHO III</td>
<td>1 (11)</td>
<td>3 (12)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>GN WHO IV</td>
<td>5 (56)</td>
<td>8 (32)</td>
<td>3 (43)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>GN WHO V</td>
<td>1 (11)</td>
<td>3 (12)</td>
<td>1 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Observation period, mean±SD months</td>
<td>19±18</td>
<td>21±9</td>
<td>29±25</td>
<td>19±10</td>
</tr>
</tbody>
</table>

aThere were no significant differences in disease activity (SIS), sex, age, disease duration, duration of the observation period or major organ involvement, apart from more patients with renal disease in group B than group D (p<0.02). GN glomerulonephritis.
reinfused into the patient via a contralateral vein. Calcium gluconate was infused at a rate of 6 mmol/h to avoid citrate-induced hypocalcaemia. Two columns were assigned to each patient and stored under sterile conditions between the IAS sessions [13, 27].

One cycle of IAS consisted of two consecutive treatment sessions within three days. During the first month of treatment, IAS was performed at an average of 3±1 sessions/week (mean±SD). Subsequently, in accordance with clinical improvement, the frequency of IAS sessions per patient was slowly reduced to one cycle followed by a treatment-free interval of two weeks, leading to an average of 1±0 session/week during the last month of observation.

**Intravenous cyclophosphamide pulse therapy (IVCP)**

The standard regimen of IVCP therapy consisted of 0.5–0.75 g/m² in 250 ml of 0.9% saline infused at intervals of 4 weeks for the initial 3–6 months [28], and thereafter every third month until disease activity had markedly and persistently decreased. If neuropsychiatric manifestations were the indication for IVCP, this therapy was stopped before the third bolus if adequate disease control was achieved. Concomitant i.v. or oral MESNA (uromitexan) treatment was given as prophylaxis against bladder toxicity.

**Testing for systemic infection**

Whenever infections were suspected clinically, attempts were made to characterise the infective agent. Bacteria (and fungi) were identified from blood, stool and/or urine cultures as appropriate, or by needle aspiration and/or swab in case of localised infections. Where bacterial isolates were not available, as in pneumonia, infection was confirmed from clinical findings in combination with radiographic evaluation and response to antibiotics. Complement fixation test, indirect immunofluorescence, enzyme immunoassays, and/or polymerase chain reaction were used for the detection of viral infections. Infections were regarded as severe if they necessitated hospitalisation and/or specific intravenous treatment. Minor infections were defined as those that did not require hospitalisation and which resolved under oral therapy [18].

**Statistical analysis**

All group results were expressed as mean±SD. Paired Student’s t-test, Student’s t-test, and Fisher’s exact test (2-tailed) were used for comparison of individual paired values, group values, and discriminatory parameters, where appropriate. If logarithmic transformation resulted in distributions more closely following Gaussian curves, such transformation was performed. P values less than 0.05 were considered significant.

**Results**

**Infections**

**Bacterial infections**

Among patients in group B (IAS only, moderately active disease at baseline), there was no evidence for even a single episode of severe bacterial infection as defined in the methods section (Fig. 1). Two of the 15 (13%) control patients with comparable disease activity, group D, suffered from severe infections (0 vs. 0.1 severe infection per patient year of observation, p=n.s.). Similarly low numbers (p=n.s.) of minor infections were observed in groups B (n=1) and D (n=1) (0.06 vs. 0.05 per patient year, p=n.s.). Details of the infections are shown in Table 3.

In contrast to the patients in groups B and D, 3 of 9 in group A (33%) and 5 of 25 in group C (20%) had severe bacterial infections (0.21 vs. 0.21 severe infections per patient year of observation, p=n.s.) (Fig. 1). Although the difference between groups A and C was not significant, when grouped together, based on their highly active disease and IVCP therapy with or without IAS, they had more frequent severe bacterial infections than groups B and D combined (24% vs. 9%, respectively, p<0.04). Differences in minor infections between groups A and C were not significant (3 of 9 [33%] vs. 5 of 25 [20%], respectively, or 0.21 vs. 0.16 per patient year, p=n.s.). Details of infectious episodes are shown in Table 3.

All three episodes of severe bacterial infections during IAS treatment occurred among the patients with highly active disease who received additional IVCP (group A). One of these patients, who had missed all clinical appointments for months, had been admitted in critical condition with a severe flare of his SLE. His condition worsened despite IVCP, high-dose glucocorticoids, and 10 sessions of IAS; he finally died of *Pseudomonas* spp. septicaemia three weeks after admission. Another patient in group A (IAS+IVCP) developed *Clostridium difficile* enterocolitis after oral antibiotic therapy for a minor staphylococcal paronychia. The third patient in this group developed pneumonia. Among patients in group C (IVCP only), five patients developed a total of nine severe bacterial infections, as detailed in Table 3.

**Fig. 1.** Patients with severe infections. Comparison of the two groups with highly active, IVCP-treated disease found no life-threatening viral infection and episodes of herpes zoster were equally distributed. There was no significant difference in the occurrence of severe bacterial infections (33% in group A vs. 20% in group C, p=n.s.). Among the patients with moderately active, IAS-treated disease who did not receive additional IVCP (group B), there was no evidence of any severe viral or bacterial infection. In the similarly active group D, there were no viral infections and the number of patients with severe bacterial infections was low (2/15 [13%], p=n.s.)
No life-threatening viral infection

No potentially life-threatening viral infection was seen in any of the patients treated with IAS. Episodes of herpes zoster eruptions were distributed similarly among groups A and C (1 of 9 [11%] and 3 of 25 [12%], respectively, p = n.s.; 0.07 vs. 0.07 episodes per patient year, p = n.s.) (Fig. 1, Table 3). No viral disease was seen among group B patients.

Analysis of major risk factors for infection

Recently, both prospective [18] and retrospective studies [29] of SLE, with 200 and 87 patients respectively, have outlined several factors that increase the risk of infections. These included highly active disease, renal involvement, and therapy with either pulse IVCP or glucocorticoids. Accordingly, we analysed these factors and again compared the two groups with high disease activity and the two with moderately active disease.

High disease activity and renal involvement

As detailed in the patients section and summarised in Table 2, disease activity and organ involvement were similar in groups A and C and in groups B and D, with the exception of more frequent renal involvement in group B than in group D (71% vs. 20%, respectively, p < 0.02); however, this did not influence the risk of infection. As shown in Table 4, the degree of proteinuria was similar among patients in groups A, C, and B. However, more pronounced impairment of renal function, as revealed by higher creatinine levels in groups A and C than in group B, may have contributed to higher susceptibility to infection, but IAS did not appear to enhance this risk.

Pulse cyclophosphamide therapy

In line with the persistently high activity of their disease despite IVCP therapy as the indication for starting IAS treatment, patients in group A had received higher total doses of IVCP than group C patients before the start of observation (cumulative dose 2.7 ± 4.4 g vs. 0.8 ± 1.7 g, p < 0.04, Table 4). During observation, patients in group A received an additional 2.9 ± 2.7 g IVCP (4 ± 3 pulses) and group C 4.4 ± 2.2 g IVCP (6 ± 3 pulses, p = n.s.). Overall, groups A and C received similar total doses of IVCP (5.6 ± 4.4 g vs. 5.2 ± 2.4 g, respectively, p = n.s.). The two IVCP-treated groups had similar leukocyte nadirs (Table 4). Thus, given the similarities in infection rates, it appears that IVCP rather than IAS may have contributed to the occurrence of bacterial and viral infections among patients receiving IVCP or IVCP + IAS.

Glucocorticoids

All patients received oral glucocorticoids [30] during the observation period, the mean dose of which was similar in groups A, C and B (31 ± 19, 25 ± 34, 27 ± 13 mg, respectively). Patients in group D received lower doses (11 ± 9 mg) than group B (p < 0.01). These findings were also reflected in comparisons of cumulative steroid doses in groups A and C (13.4 ± 1.6 g vs. 13.6 ± 17.1 g, p = n.s.) and groups B and D (21.4 ± 23.9 g vs. 5.1 ± 3.2 g, p < 0.05). Thus, it appears that glucocorticoids did not contribute to the risk of infection. There were no differences between the groups regarding other immunosuppressive therapies.
Other risk factors for infection

As detailed in the methods section, both IAS and IVCP were usually administered via peripheral veins, but a central venous device (CVD) was implanted if haemodialysis became necessary or when patients were admitted to an intensive care unit. In group A, 5 of the 9 [56%] patients required a CVD at least once, two of them having more than one instance of CVD implantation (2 and 3, respectively), and two patients developed bacterial infections while having a CVD. In group C, 6 of the 25 [24%] patients received CVDs and one experienced an infection during this time. There was only one CVD implantation in group B [14%]; no infection) and none in group D. Statistical analysis did not reveal significant differences.

At the beginning of the observation, serum levels of IgG, IgA and IgM were within normal ranges in each group (data not shown).

### Disease activity at baseline and therapeutic response

The response to therapy is shown in Fig. 2. At baseline, the mean disease-activity score (SIS) of all patients who received IAS (groups A plus B, n = 16) was 13 ± 5. The mean SIS in patients in group A (IAS + IVCP, n = 9) was 16 ± 5, indicating highly active disease; at the end of the observation period (19±18 months), their SIS had decreased to 4 ± 3 (p < 0.0001). Mean SIS in group C, i.e. patients with highly active disease not treated with IAS (IVCP only, n = 25), was 16 ± 5 at baseline, decreasing to 5 ± 3 after a mean of 21±9 months of observation (p < 0.0001). Among patients with moderately active disease (group B; IAS only, n = 7), the mean SIS was 9 ± 3 at the start and 3 ± 1 after 29±5 months (p < 0.005). The control group with similarly moderate disease (group D; neither IAS nor IVCP, n = 15) had an initial SIS of 9 ± 3, which improved to 5 ± 3 (p < 0.005) after a mean of 19±10 months of observation. Moreover, although all patients in group A had not sufficiently responded to IVCP alone, all but one improved to moderate or even low activity of disease when given IAS+IVCP.

### Decreased levels of anti-dsDNA antibodies and increased levels of complement

Serum levels of anti-dsDNA auto-antibodies were determined before administration of IVCP and before the
start of the respective cycle of IAS. Levels in group A decreased from 454 ± 746 IU/ml at the start of IAS therapy to 16 ± 12 at the end of observation (p = 0.002), and in group B (IAS only) from 184 ± 256 to 21 ± 20 IU/ml. In group C (IVCP only), levels decreased from 332 ± 256 to 16 ± 4 (p = n.s.). Levels of C4 slightly increased in all groups (p = n.s., data not shown).

**Extended observation period**

One year after the end of observation for this study, nine patients are still undergoing IAS therapy with stable disease. A very young patient was withdrawn and later went on to autologous stem-cell transplantation because of recurrent pneumonitis despite high-dose IVCP treatment [31]. One patient with clinically active SLE withdrew her consent after 18 sessions of IAS, left the country and was subsequently lost to follow-up. IAS therapy was discontinued in four patients after stabilisation of lupus activity and marked clinical improvement.

**Discussion**

The two major causes of death among SLE patients are infections and relentlessly progressive disease [14–16]. Infectious complications are therefore a major concern when treating active SLE, and this concern is even greater when extracorporeal treatment is used [4]. Thus, evaluation of infections associated with new extracorporeal treatment techniques is of significant importance.

Since IAS is an expensive and still experimental treatment and since its safety and efficacy in SLE have not yet been sufficiently documented, IAS has been used in our patients mainly as a last therapeutic resort when they continued to have highly active or even progressing disease refractory to steroids and IVCP therapy, or when IVCP was contraindicated. Thus, most of the patients undergoing IAS therapy constituted a "negatively" selected "high-risk" population. Since patients with a serious course of SLE treated with PE+IVCP are at increased risk of severe infections (CMV and one case of mumps pancreatitis) [4], patients on IAS would be regarded as having greater susceptibility to infectious diseases because of both their high disease activity [18–22] and their past use of pulse IVCP, in conjunction with an extracorporeal procedure in some of them [4, 18, 23, 29]. In fact, in the present analysis, patients with highly active disease and ongoing IVCP treatment – irrespective of IAS – had higher rates of severe bacterial infections than patients with low activity of disease not requiring IVCP currently, even if they had been treated with pulse IVCP in the past.

Thus, in our study disease activity and IVCP therapy were associated with a higher propensity to develop severe bacterial infections, as expected [29]: 89% of all severe infections were observed in the two groups with highly active disease treated with IVCP (A and C). There were no significant differences in rates of infection between groups A (IAS+IVCP) and C (IVCP alone).

Importantly, while patients in groups A (IAS+IVCP) and B (IAS only) had both received high doses of IVCP prior to IAS therapy (Table 4), only those patients who were given IVCP during the observation period, with or without concomitant IAS, developed serious infections. Although we observed one case of fatal bacterial infection in a patient in group A (IAS+IVCP), this appeared related to the patient’s low compliance and consequent high disease activity, which became life threatening prior to IVCP and the IAS procedures. Moreover, IAS was safely used in one patient with active tuberculosis, a disease with growing importance in industrialised countries, where aggressive immunosuppressive therapies are contraindicated [12, 32, 33]. Together, these data indicate that IAS per se does not increase the infectious risk brought about by high disease activity and IVCP treatment.

Indeed, IAS in patients without concomitant IVCP appeared safe with regard to infectious disease. The seven patients receiving IAS alone did not suffer from even a single episode of severe infection. Moreover, even when those receiving IAS + IVCP were included, none of the IAS patients had episodes of life-threatening viral infection (Table 3), which is in sharp contrast with previous findings in SLE patients treated with PE and IVCP [4].
Previous observations on extracorporeal therapy in SLE reported a higher [4, 34, 35] or equal [36] risk of infection when combined PE and IVCP treatment was compared with standard IVCP, but with severe infections and cases of infection-related death also occurring in the latter trial. In addition, a retrospective study identified PE as a risk factor for infections in SLE [29]. In this respect, IAS may be better than PE for several reasons: (i) the re-infusion of autologous plasma avoids the need for substitution of fluid and proteins and may thus prevent the transfer of infectious agents, as reported in PE [37, 38]; (ii) the selective removal of Ig and IC limits changes in the immune system compared with the non-specific removal of all plasma components, since many molecules involved in defence, particularly those involved in innate immunity, are reinfused [11]; and finally, (iii) in contrast to PE, and as shown here, IAS may not necessarily require all patients to have additional IVCP treatment, thus further reducing the risk of infections.

The data analysed suggest that IAS is highly effective in SLE. The highly active disease of group A patients was significantly reduced to low or moderate activity by IAS plus IVCP. Importantly, these patients had been given high doses of IVCP prior to the start of IAS, and the high baseline activity of their disease reflects the failure of IVCP alone, which may thus serve as an internal control for their response to IAS in combination with IVCP. In addition, patients with moderately active disease improved well on IAS combined with glucocorticoids and/or additional non-cytotoxic immunosuppressants.

In summary, although the present study is limited by the uncontrolled, compassionate use of IAS and the retrospective rather than controlled prospective analyses, the data obtained from the tightly matched control populations allow the conclusion that IAS is a safe and probably effective procedure for SLE patients whose disease is refractory or where there are contraindications for traditional immunosuppressive treatments. However, the true efficacy of IAS can only be determined in controlled clinical trials. Based on the data presented, such a trial of IAS treatment efficacy appears appropriate for determining the place of IAS in the treatment of SLE and, in particular, whether this treatment truly constitutes a new option for patients with refractory disease.

References


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