Efficacy of plasma exchange and immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome: A systematic review

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Abstract

Extracorporeal treatments have been used since the 1970s in the management of systemic lupus erythematosus (SLE). A randomised controlled trial comparing the efficacy of standard of care (SOC) combined with plasma exchange against SOC alone in patients with lupus nephritis revealed no difference in terms of renal outcome. Subsequently, initial expectations have been dampened and further experience with plasma exchange is mainly limited to observational studies and single case reports. Beneficial effects have been reported in patients with refractory disease course or in pregnancy with prior complications due to SLE and antiphospholipid syndrome. A more specific form of extracorporeal treatment, immunoadsorption (IAS), has emerged as a valuable option in the treatment of SLE. In line with the plasma exchange experience, IAS seems to have beneficial effects in patients with refractory disease, concomitant to standard immunosuppression or during pregnancy. The mechanism IAS relates to autoantibody removal but for plasma exchange removal of activated complement components, coagulation factors, cytokines and microparticles may also be relevant. Both treatment forms have good safety profiles although reactions to blood product replacement in plasma exchange and procedure related complications such as bleeding or catheter-related infections have occurred. There is a need to more clearly define the clinical utility of plasma exchange and IAS in refractory lupus and APS subgroups.

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1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with heterogeneous clinical manifestations and disease course. With the advent of combination glucocorticoid and immunosuppressive therapy, the prognosis of patients has improved [1]. However, those lacking a good response to standard therapy, classified as ‘refractory SLE’, remain a therapeutic challenge. Definitions of refractory disease are inconsistent: in lupus nephritis, this can comprise progressive deterioration of renal function, persisting nephrotic syndrome and a failure to achieve a partial proteinuric response by 12 months or complete response by 24 months [2]. Such definitions do not exist for other severe or life-threatening disease manifestations, such as refractory cutaneous, neuropsychiatric or haematological SLE. Current guidelines recommend excluding PLEX as a treatment option in refractory mononeuritis multiplex or central nervous system vasculitis secondary to SLE only [5].

Extracorporeal treatments such as PLEX and IAS are used in other antibody-mediated disorders, such as myasthenia gravis, idiopathic dilated cardiomyopathy, gomerular disorders (i.e. ANCA-associated vasculitis, focal segmental glomerulosclerosis or anti-GBM disease) and in patients undergoing desensitisation before renal transplantation [6]. An older trial conducted by the Lupus Nephritis Collaborative Study Group (LNCSG) comparing PLEX in combination with cyclophosphamide (CYC) and steroids to standard therapy alone revealed no improvement in renal outcome [7]. A report by the Lupus Plasmapheresis Study Group (LPSG) indicated long-term remission in 8 of 14 patients undergoing PLEX with subsequent CYC administration (‘synchronised’ therapy) [8]. Results of their multicentre randomised controlled trial were never communicated. The Dutch Co-operative Study Group compared PLEX in combination with steroids to standard treatment and found no superiority of cytotoxic treatment to PLEX in patients with lupus nephritis [9]. Similar results were corroborated by a small controlled study from Japan [10]. No trials comparing efficacy of IAS either with or without other immunosuppressive measures against a comparator group have been conducted so far. In this review, we focus on principles of PLEX and IAS in SLE and the efficacy of both extracorporeal treatments in clinical trials and observational studies.

2. Methods

2.1. Search strategy

A systematic literature search of the MEDLINE database was conducted, using the key words: “(immunoadsorption OR plasmapheresis) AND (antiphospholipid syndrome OR APS OR catastrophic antiphospholipid syndrome OR CAPS OR lupus nephritis OR LN OR systemic lupus erythematosus OR SLE)”.

The search was limited to articles reporting on at least five patients undergoing IAS and ten patients undergoing PLEX. Comments to articles, review articles or reports including mainly patients in remission and comparing different IAS columns were not included. Additional studies were identified by examining the bibliography of the retrieved articles by forward search.

3. Results

3.1. Search results

The systematic search (performed on December 1st, 2014) resulted in 130 records reporting on IAS treatment in SLE, lupus nephritis, antiphospholipid syndrome (APS) or its catastrophic variant. 112 articles were excluded, since these reported on single cases, case series with a total number below five, reviews, non-English publications and one publication comparing different columns [11] in patients with remission and one article could not be assessed in full text [12]. A lack of clinical data and/or publication of in vitro results led to the exclusion of another six articles [13–18].

Due to more publications reporting on PLEX treatment in SLE, the arbitrary cut-off for inclusion was set to at least 10 treated patients. We excluded 997 articles due to reporting single cases or case series with fewer than 10 patients, reviews, non-English publications, several non-related case reports/series and two were not accessible in full text [19,20]. Through forward search of the retrieved bibliography we identified another two eligible records. Seven articles were excluded due to not evaluating efficacy of PLEX despite treating at least ten patients [21–24], PLEX treatment in a ‘steady’ state with no obvious indication to initiate additional immunosuppression [25], in vitro experiments [26] and review of the literature [27]. Thus, a total number of 15 articles reporting on PLEX treatment were included.

3.2. Removal of disease-specific antibodies and immunologic alterations following extracorporeal treatment

3.2.1. Plasma exchange

3.2.1.1. Anti-nuclear antibodies and anti-double stranded DNA antibodies

Analysis of an older cohort revealed a decline of both anti-nuclear antibody titre (ANA) from an initial value of 640 (40–2560) to 160 (0–1280) and anti-double stranded DNA (dsDNA) antibody titre from 40 (0–160) to 0 (0–20) after PLEX [28]. After a mean of 1.15 months, another single centre report indicated anti-dsDNA antibody negativity in all patients [29]. In an observational study, anti-dsDNA antibodies decreased from 113 ± 31 to 23 ± 11 U/ml [30], whereas others observed a halving of anti-dsDNA antibodies (48.87 ± 28.9 to 25.7 ± 29.96) in a cohort with lupus nephritis [31]. A prospective randomised controlled trial revealed a similar decrease in anti-dsDNA antibodies in the PLEX-treated arm compared to the comparator group [7]. A fourfold reduction in anti-dsDNA antibodies was reported in patients with lupus nephritis [32]. ’Synchronised’ therapy, characterised by PLEX with subsequent administration of CYC to cover a potential antibody rebound,
led to a sharp decrease of ANA IgG, which remained low during follow-up [8]. Reductions in anti-dsDNA antibody levels were observed in patients either receiving intravenous CYP or PLEX without cytotoxic agents. In the PLEX group, anti-dsDNA antibodies decreased from 148 ± 76 to 74 ± 46 IU/mL. After an observational period of six months, anti-dsDNA antibody levels remained at a post-treatment level [10]. Anti-dsDNA antibody levels fell in both groups in an open trial comparing ‘synchronised’ therapy with pulse CYP in the treatment of proliferative lupus nephritis [33]. Patients receiving ‘synchronised’ therapy achieved the highest probability to become anti-dsDNA antibody negative and overall the decline was greater compared to patients with PLEX or intravenous CYP alone. [34]. A decline in ANA titres was observed in both trial groups comparing PLEX against IAS combined with SOC in patients with lupus nephritis [35]. There were notable differences in serological methods between studies that preclude summary conclusions on the magnitude of autoantibody change after treatment.

3.2.1.2. Complement. Restoration of complement C3 and C4 to normal levels, as well as C1q binding assay negativity could be observed in early observational studies [29,36]. These findings were corroborated by Wallace et al. who found a restoration of complement C3 (63.48 ± 3.2). Another observational study reporting on efficacy of ‘synchronised’ therapy [8]. An increase in total complement from 16 ± 4.2 to 27.9 ± 4.6 U/ml was observed in patients with lupus nephritis [10]. ‘Synchronised’ therapy led to a comparable improvement in complement C3, C4 and CH50 levels when compared to a CYC-treated group [33]. Another observational study found a normalisation of serum complement in all patients, with the highest increase of CH50 in patients treated with the ‘synchronised’ approach [34].

3.2.1.3. Other immunologic changes. A decrease in circulating immune complexes (CIC) from 71 ± 24 to 14 ± 5 μg/ml was reported by Vangelista and colleagues [30]. This finding is in line with another observational study in lupus nephritis, when a 68.5% decrease in CIC could be achieved [32]. Moreover, an improvement of lymphocyte function during PLEX and an increase in E rosette forming cells was observed [30]. A similar decline in total immunoglobulin G (IgG) and cryoglobulins was reported in PLEX-treated patients compared to the SOC group alone [7]. A sharp transient decrease in total IgG was observed in patients with refractory disease [8]. Soluble CD40 ligand, increased during active SLE, decreased following PLEX to a greater degree than IgG or albumin following a single PLEX treatment [37]. In pregnant women with either primary or secondary APS undergoing PLEX a decline in anticardiolipin IgG and IgM antibodies, along with an increase in thrombocytes and normalisation of the activated partial thromboplastin time was observed [38]. In patients with SLE and autoimmune thyroid disease, thyroglobulin antibodies and thyroid peroxidase antibodies showed a rapid and persistent decrease from an initial level of 691.86 ± 257.64 to 22.93 ± 15.22 IU/mL and 685.86 ± 236.14 to 17.42 ± 14.22 IU/mL, respectively [39]. Urinary podocyte excretion was similar in patients with lupus nephritis either receiving PLEX or cytotoxic agents in combination with steroids. In the PLEX group, urinary podocytes decreased from 3.2 ± 0.7 to 0.4 ± 0.2 cells/mL [10]. In vitro analyses revealed an increased erythrocyte immune complex binding activity, along with a restoration of erythrocyte complement receptor type 1 following PLEX treatment [26]. In patients with refractory disease, three sessions of PLEX resulted in an increase of interferon-γ positive T-helper cells, while the number of interleukin (IL)-4 and IL-10-expressing CD4⁺ T-cells decreased [40]. In active disease, the absolute number of peripheral CD4⁺ CD25(high)FoxP3⁺ T-cells was lower when compared to healthy controls. Repeated PLEX in five patients induced an increase in peripheral CD4⁺ CD25(high)FoxP3⁺ T-cells, which was paralleled by a decrease in disease activity [41] (Table 1 and Fig. 1).

3.2.1.4. Conclusion. Taken together, a reduction in the concentration of serum immunoglobulins of approximately 60% using new devices is achieved after 2–4 sessions [42] and may be accompanied by a similar reduction in CIC, ANA, anti-dsDNA and antiphospholipid antibodies. Moreover, a restoration of complement components was observed, along with an increase in erythrocyte complement receptor type 1. An increase in interferon-γ positive T-helper cells and CD4⁺ CD25(high)FoxP3⁺ T-cells and a decrease in IL-4 and IL-10-expressing CD4⁺ T-cells may explain clinical efficacy of PLEX. scD40L, a marker for active disease decreased after extracorporeal treatment.

3.2.2. Immunoadsorption

3.2.2.1. Anti-nuclear antibodies and anti-double stranded DNA antibodies. An uncontrolled study to evaluate the efficacy of IM-P® (phenylalanine ligand) revealed a reduction in anti-dsDNA antibodies by 33.9 ± 5.3% [43]. The adsorbing ratio of anti-dsDNA antibodies was 55.6 ± 4.6% in patients treated with Selesorb® columns (dextran sulphate ligand), although a ‘rebound’ phenomenon was observed after treatment [44]. In another study, the reduction in anti-dsDNA antibodies paralleled clinical efficacy when Selesorb® was used [45]. Treatment with Immunosorba® (Staphylococcus protein A as ligand) led to a decrease of anti-dsDNA antibodies from 522 [148–2000] to 177 [8–721] U/ml and anti-dsDNA-IgG3 antibodies [46]. Adsorption rate for anti-dsDNA antibodies was 58.0 ± 9.7% per session using Immunosorba® (tryptophan as ligand) columns, leading to a decrease of anti-dsDNA titres from 79.5 ± 97.7 U/ml pre-treatment to 6.6 ± 5.8 U/ml 12 months post-treatment [47]. In a prospective, controlled trial to evaluate efficacy of two different IAS columns, IM-P®-3500® (phenylalanine ligand) and lg-Therasorb® (anti-IgG antibodies as ligand) led to a comparable decline in anti-dsDNA antibodies [48]. A reduction in anti-dsDNA antibodies of 67 ± 14% was observed following treatment of nine SLE patients with lg-Therasorb® [49]. In their study recruiting patients with either failure of or contraindication to CYC, Stummvoll et al. treated 16 patients with lg-Therasorb® and found a reduction of anti-dsDNA antibodies from 391 to 53 IU/ml after 12 months [50,51]. More recently, Stummvoll and colleagues reported short (~12 months) and long-term (~12 months) results of patients undergoing IAS with lg-Therasorb® or Globaffin® (synthetic peptide Gam 146) columns. A reduction of anti-dsDNA antibody levels from 168 ± 205 to 45 ± 34 IU/ml was reported. A trend for further reduction of anti-dsDNA antibodies was reported for patients undergoing prolonged IAS [52]. Lupusorb® (VRT-101 as ligand) treatment in patients with mild disease activity led to a decline of anti-dsDNA antibodies by 46.7% [53].

3.2.2.2. Complement. IM-P® treatment led to a increase of C3c to 76.6 ± 3.9% and C4 to 54.9 ± 3.8% and a reduction of C1q IgG immune complexes by 41.9 ± 3.5%, respectively [43]. Normalisation of CH50 levels was achieved in all patients undergoing Selseorb® treatment, whereas reduction in C1q-bearing immune complexes was inconsistently reported [44]. Complement C3/C4 remained unchanged following IAS with Miro®, while anti-C1q antibodies became undetectable with the exception of one patient [54,55]. Complement normalisation was achieved with the exception of one patient with congenital C4 deficiency in patients receiving Immunorsorba® treatment [46]. Ig-Therasorb® treatment in patients with lupus nephritis led to an increase of C3c from 0.5 to 0.8 g/l and C4 from 0.1 to 0.2 g/l [51]. Complement C3 and C4 remained stable over time during follow-up of patients treated with Lupusorb® [53]. The removal of the anaphylatoxins C3a and C4a with Selseorb® was analysed in vitro by Matsui et al., who showed a reduction of C3a and C4a from the separated plasma (from 775 ± 334
Characteristics of patients treated in observational and prospective trials with plasma exchange are depicted. The name of the respective primary author, the year of publication in a chronologic order, the number of patients undergoing plasma exchange (and the concomitant treatment strategy) are listed.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number (refractory to standard)</th>
<th>Outcome parameter</th>
<th>Clinical efficacy (including proteinuria)</th>
<th>Efficacy (laboratory - disease activity assessment tool)</th>
<th>Disease flare</th>
<th>Follow-up (months)</th>
<th>Organ manifestation</th>
<th>Side effects</th>
<th>Concomitant IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blaszczyk</td>
<td>1981</td>
<td>11 (0)</td>
<td>'Improvement' remission, ANA, anti-dsDNA AB</td>
<td>Remission (9%), improvement (73%), no improvement (18%)</td>
<td>Reduction in ANA (82%), reduction in anti-dsDNA AB (82%)</td>
<td>36.3%</td>
<td>0.5–36</td>
<td>K (64%), A (27%), MC (36%), S (27%), H (18%), R (18%), C (9%)</td>
<td>Not stated</td>
<td>Steroids (11), CYC (1), AZA (3)</td>
</tr>
<tr>
<td>Lewis</td>
<td>1982</td>
<td>32 (0)</td>
<td>Kidney function, haemodialysis, death</td>
<td>Creatinine improved from 1.93 (± 1.9) to 1.56 (± 1.0), ESRD (9.4%)</td>
<td>–</td>
<td>Not stated</td>
<td>9</td>
<td></td>
<td></td>
<td>Death (9.4%)</td>
</tr>
<tr>
<td>Lewis</td>
<td>1982</td>
<td>10 (10)</td>
<td>Kidney function, C3/C4, anti-dsDNA AB</td>
<td>Creatinine improved from 2.1 (± 1.4) to 1.2 (± 0.5)</td>
<td>C3/C4 and C1q restored to normal values, anti-dsDNA negative</td>
<td>Not stated</td>
<td>11.5 (± 7)</td>
<td>K (100; LN IV 70%, V 20%, II 10%)</td>
<td>Death (20%) (active SLE and opportunistic infection)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Vangelista</td>
<td>1983</td>
<td>11 (0)</td>
<td>Kidney function, proteinuria, CIC, anti-dsDNA AB</td>
<td>Kidney function (improved 91%), proteinuria (1–4.5 initial to 0.1–2.2)</td>
<td>–</td>
<td>Not stated</td>
<td></td>
<td></td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Wei</td>
<td>1983</td>
<td>10 (0)</td>
<td>'Activity score', serologic changes</td>
<td>50% improvement of the activity score (50%)</td>
<td>Reduction in anti-naïve DNA and C1q binding activity</td>
<td>Not stated</td>
<td>1.5</td>
<td>MC (80%), S (30%), mental changes (50%)</td>
<td>Not stated</td>
<td>Steroids (number unclear), CQ/HQ (number unclear) Ongoing therapy</td>
</tr>
<tr>
<td>Wallace</td>
<td>1988</td>
<td>17 (17)</td>
<td>'Response'</td>
<td>Good response (41%), poor response (29%)</td>
<td>–</td>
<td>Not stated</td>
<td>24</td>
<td>K (100%)</td>
<td>Not stated</td>
<td>Steroids (100%)</td>
</tr>
<tr>
<td>Lewis a</td>
<td>1992</td>
<td>40 (0)</td>
<td>Time to death, renal failure/dialysis, anti-dsDNA AB, C3/C4</td>
<td>No significant difference *, complete renal remission (30%), renal failure (35%)</td>
<td>Anti-dsDNA AB decline significant (w2/3/5) *, C3/C4 with initial significant decrease</td>
<td>Not stated</td>
<td>32</td>
<td>K (100; III 23%, IV 40%, V 37%)</td>
<td>Not stated</td>
<td>Steroids, CYC (100%)</td>
</tr>
<tr>
<td>Lombardo</td>
<td>1993</td>
<td>37 (not stated)</td>
<td>'Improvement'</td>
<td>Improvement (at least 54%)</td>
<td>–</td>
<td>Not stated</td>
<td>Not stated</td>
<td>K (35%), H (11%), N (5%), APS (8%), HP (5%), V (35%)</td>
<td>Not stated</td>
<td>Steroids, CYC (100%)</td>
</tr>
<tr>
<td>Euler</td>
<td>1994</td>
<td>14 (14)</td>
<td>SLAM, proteinuria, ANA</td>
<td>28.4 (pre-treatment) to 8.9 (SLAM), proteinuria from 5.8 to 2.7 g/d</td>
<td>ANA IgG from 1.2:560 to 1:160</td>
<td>28.6% (mean follow-up 6 years)</td>
<td>6</td>
<td>K (71%, IV 21%, III 14%), A (93%), MC (93%), S (71%), C (7%), P (21%), HS (50%)</td>
<td>Amenorrhea (29%), HZV (36%), haematologic alteration (100%), death (7%)</td>
<td>Steroids, CYC (100%)</td>
</tr>
<tr>
<td>Nakamura</td>
<td>2002</td>
<td>10 (10)</td>
<td>Proteinuria, anti-dsDNA AB, complement, urinary podocytes</td>
<td>Proteinuria (p &lt; 0.001 to controls, n.s. between groups *)</td>
<td>Anti-dsDNA AB, complement, urinary podocytes (p &lt; 0.001 to controls, n.s. between groups)</td>
<td>Not stated</td>
<td>6</td>
<td>K (IV, 100%), A (40%), MC (70%), S (100%), H (60%), C (100%)</td>
<td>Not stated</td>
<td>Steroids</td>
</tr>
<tr>
<td>Danielli</td>
<td>2002</td>
<td>12 (0)</td>
<td>CR/PR, proteinuria, anti-dsDNA AB</td>
<td>75% CR, 25% PR (p &lt; 0.02) *, proteinuria “improved”</td>
<td>Anti dsDNA AB improved</td>
<td>33.3%</td>
<td>6/48</td>
<td>K (100, IV 75%, V 25%)</td>
<td>Steroids, CYC (100%)</td>
<td>Steroids</td>
</tr>
<tr>
<td>Kimura</td>
<td>2005</td>
<td>10 (not stated)</td>
<td>SLEDAI, scDC40L</td>
<td>SLEDAI (significant decrease)</td>
<td>scDC40L (p = 0.0251)</td>
<td>Not stated</td>
<td>9.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-Hagie</td>
<td>2007</td>
<td>18 (18 pregnancies)</td>
<td>Live birth (APS), aCL AB, proteinuria</td>
<td>SLEDAI (significant decrease)</td>
<td>scDC40L (p = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamaji f</td>
<td>2008</td>
<td>13 (13)</td>
<td>CR/IR, anti-dsDNA AB</td>
<td>69.2% (CR), 23.1% (IR)</td>
<td>Anti-dsDNA AB (p &lt; 0.05) compared to pulse CYC group</td>
<td>7.7%</td>
<td>60</td>
<td>K (100; IV 38.5%, other types 23.1%, no biopsy 38.3%)</td>
<td>Not stated</td>
<td>Steroids, CYC (100%)</td>
</tr>
</tbody>
</table>

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3.2.2.3. Other immunologic changes. A moderate reduction of total IgG by 18.3 ± 3.1% was achieved by IM-P® treatment [43]. Reduction of immunoglobulins was reported in an open trial using Miro® [54,55]. Gaubitz et al. found a similar decrease of total IgG following IMPH-350® and Ig-Therasorb® treatment, which returned to pre-IAS levels 4 weeks thereafter [48]. The first cycle of Ig-Therasorb® IAS in patients with lupus nephritis led to undetectable serum IgG levels (<1.95 g/l) in 75% of patients, reducing mean serum IgG from 9.72 to 2.11 g/l [45,46]. A subset of patients included in the latter cohort with detectable anticardiolipin antibodies was analysed separately. A single session of IAS reduced the concentration of anticardiolipin IgG and IgM antibodies by 62.94 ±

to 640 ± 252 ng/ml, and from 1,303 ± 847 to 619 ± 578 ng/ml, respectively) [13].

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number (refractory to standard)</th>
<th>Outcome parameter</th>
<th>Clinical efficacy (including proteinuria)</th>
<th>Efficacy (laboratory – disease activity assessment tool)</th>
<th>Disease flare</th>
<th>Follow-up time (months)</th>
<th>Organ manifestation</th>
<th>Side effects</th>
<th>Concomitant IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loo</td>
<td>2010</td>
<td>14 (0)</td>
<td>SLEDAI, proteinuria, creatinine, ANA</td>
<td>SLEDAI (significant), proteinuria (significant) and creatinine (improved)</td>
<td>Decline in ANA titres</td>
<td>3 (21.4%)</td>
<td>K (100%, class III, IV ± V)</td>
<td>TP (n = 3)</td>
<td>Steroids, CYC, IVIG (14)</td>
<td></td>
</tr>
<tr>
<td>Liu</td>
<td>2011</td>
<td>11 (11)</td>
<td>SLEDAI, proteinuria, TPO AB, TG AB</td>
<td>SLEDAI (p &lt; 0.001), proteinuria (p = 0.0077)</td>
<td>TPO AB, TG AB (p = 0.001)</td>
<td>Not stated</td>
<td>12</td>
<td>AITD (100%), K (54.5%; II, IV, V 9.1% each, III 18.2%), hepatitis (9.1%)</td>
<td>Local bleeding at the site of catheter insertion due to TP (18.2%)</td>
<td>Steroids, CYC (switched to MMF after response)</td>
</tr>
</tbody>
</table>

a Good response (normal creatinine, absence of nephrotic range proteinuria), poor response (creatinine ≥ 3 mg/dl or requiring ESRD).
b Compared to standard treatment consisting of steroids and oral CYC.
c Compared to standard treatment consisting of steroids and pulse CYC.
d Compared to patients receiving steroids and pulse CYC (31% CR, 69% PR).
e Whereas after long-term significance the difference was not significant.
f Plasma exchange group was compared to a group with pulse CYC and a group receiving pulse CYC and plasma exchange.

Fig. 1. Technical aspects and molecular changes exerted by immunoadsorption (left side) and plasma exchange (right side) in systemic lupus erythematosus.
Table 2

Characteristics of patients treated in observational and prospective studies with immunoadsorption are depicted. The name of the respective primary author, the year of publication in a chronologic order, the number of patients undergoing immunoadsorption (‘refractory cases’ in parenthesis), major clinical/laboratory outcomes with the respective alterations to baseline or compared to comparator group, rate of disease flares, the duration of follow-up, most important clinical manifestations of the disease leading to immunoadsorption, side effects attributable to immunosuppression, the concomitant treatment and the respective immunoadsorption column are listed.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number (refractory to standard)</th>
<th>Outcome parameter</th>
<th>Clinical efficacy</th>
<th>Efficacy (laboratory – disease activity assessment tool)</th>
<th>Disease flare (severe/minor)</th>
<th>Follow-up time (months)</th>
<th>Organ manifestation</th>
<th>Side effects</th>
<th>Concomitant IS</th>
<th>IAS columns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider</td>
<td>1990</td>
<td>12 (12)</td>
<td>SLAM, anti-dsDNA AB, C1q IgG CIC</td>
<td>SLAM (improved 11/12)</td>
<td>Anti-dsDNA AB, C1q IgG CIC (decreased)</td>
<td>Not stated</td>
<td>6</td>
<td>K (41.7%), H, P (8.3% each)</td>
<td>No side effects observed</td>
<td>Steroids (3), CYC (3), AZA (5), CSA (1)</td>
<td>IM-P®</td>
</tr>
<tr>
<td>Suzuki</td>
<td>1991</td>
<td>6 (0)</td>
<td>Proteinuria, lymphocyte count, anti-dsDNA AB, CH50, C1q-CIC “improvement” anti-dsDNA AB</td>
<td>5/6 proteinuria decrease, 4/6 lymphocyte count improved</td>
<td>5/6 decline in anti-dsDNA AB levels, CH50 normalisation, 4/6 decline in C1q-CIC Anti-dsDNA AB (p &lt; 0.05)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>K (100%), II, II, V 16.7%, IV 33.4%, H (100%)</td>
<td>Not stated</td>
<td>Steroids (6), bredinin (2)</td>
<td>Selesorb®</td>
</tr>
<tr>
<td>Funauchi</td>
<td>1996</td>
<td>5 (5)</td>
<td>“Improvement” anti-dsDNA AB</td>
<td>Not stated</td>
<td>Not stated</td>
<td>K (40%), MC (60%)a</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Steroids (5), CYC (1), CSA (1)</td>
<td>Selesorb®</td>
<td></td>
</tr>
<tr>
<td>Gaubitz</td>
<td>1998</td>
<td>20 (20)</td>
<td>SLAM, anti-dsDNA AB</td>
<td>8/10 Ig-Therasorb®, 5/10 IMPH-350® (&gt;30% reduction SLAM)</td>
<td>&gt;50% reduction of anti-dsDNA AB in both groups</td>
<td>Not stated</td>
<td>6</td>
<td>K (20%), H (25%), C (5%), CP (15%)</td>
<td>Anaphylactic reaction (1)</td>
<td>Steroids (18), CYC (2), AZA (4), CSA (2), CQ (9)</td>
<td>Ig-Therasorb®, IMPH-350® (each n = 10)</td>
</tr>
<tr>
<td>Hiepe/ Pfueller</td>
<td>1999/2001</td>
<td>8 (0)</td>
<td>ECLAM, C1q autoantibodies, CIC</td>
<td>CR (37.5%), PR (37.5%), NR (25%), ECLAM (significantly reduced)</td>
<td>C1q autoantibodies and CIC (significantly reduced)</td>
<td>Not stated</td>
<td>12</td>
<td>K (50%), A (50%), MC (75%), S (12.5%)</td>
<td>Not stated</td>
<td>Steroids (19)</td>
<td>Selesorb®</td>
</tr>
<tr>
<td>Suzuki</td>
<td>2000</td>
<td>19 (0)</td>
<td>SLEDAI, anti-dsDNA AB</td>
<td>Not stated</td>
<td>Not stated</td>
<td>1 (7)</td>
<td>Not stated</td>
<td>Steroids (19)</td>
<td>Selesorb®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braun</td>
<td>2000</td>
<td>8 (8)</td>
<td>SLAM</td>
<td>Not stated</td>
<td>Anti-dsDNA AB decline (no statistical calculation)</td>
<td>Relapse-free remission (50%)</td>
<td>54 ± 10</td>
<td>K (100%), A (75%), MC (37.5%), C (37.5%), CP (37.5%), HS (25%), V (50%)</td>
<td>Not stated</td>
<td>Steroids (8), oral CYC 3–6 months commenced after last IAS (8)</td>
<td>Immunosorba®</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>n (A/B)</td>
<td>Sample Description</td>
<td>Baseline Measures</td>
<td>Initial AB</td>
<td>Follow-up AB</td>
<td>Follow-up Mild Allergic Reaction</td>
<td>Follow-up Infections</td>
<td>Follow-up Steroids</td>
<td>Follow-up Immunosorba®</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Willeke 2002</td>
<td>9 (0)</td>
<td>Ab positive SLE patients SLAM, anti-dsDNA AB, IL-10 producing PBMC</td>
<td>SLAM (p &lt; 0.01)</td>
<td>Anti-dsDNA AB (p &lt; 0.05), IL-10 producing PBMC (p &lt; 0.01)</td>
<td>Not stated</td>
<td>2</td>
<td>Not stated</td>
<td>Mild allergic reaction (1)</td>
<td>Steroids (3), CYC (2), AZA (3), MMF (2), HCQ (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stummvoll/Stummvoll 2005/2004</td>
<td>16 (9)</td>
<td>Renal remission, SLEDAI, SIS, ECLAM, anti-dsDNA AB, C3c/C4</td>
<td>At least PR (64%), NR (36%). SLEDAI, SIS and ECLAM (each p &lt; 0.0001)</td>
<td>Anti-dsDNA AB (p = 0.0002), C3c/C4 (p &lt; 0.002)</td>
<td>4/3</td>
<td>12</td>
<td>Infections (n = 8, severe n = 4), anaphylactic episodes (n = 3)</td>
<td>Steroids (n = 16), CYC (n = 4), AZA (n = 3), MMF (n = 5), CQ (n = 4), MTX (n = 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugimoto 2006</td>
<td>6 (0)</td>
<td>Anti-dsDNA AB, CIC, proteinuria</td>
<td>Proteinuria (p &lt; 0.001)</td>
<td>Anti-dsDNA AB (p &lt; 0.05), IC (p &lt; 0.05)</td>
<td>Not stated</td>
<td>12</td>
<td>Not stated</td>
<td>-</td>
<td>Steroids (6), CYC (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loo 2010</td>
<td>14 (0)</td>
<td>Proteinuria, creatinine, ANA</td>
<td>SLEDAI and proteinuria (significant), creatinine (improved)</td>
<td>Significant decline in ANA titres</td>
<td>3 (21.4%)</td>
<td>6</td>
<td>TP (n = 2)</td>
<td>-</td>
<td>Steroids, CYC, IVIG (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stummvoll 2012</td>
<td>16 (b)</td>
<td>Renal remission, SLEDAI, anti-dsDNA AB</td>
<td>Anti-dsDNA AB (n.s.)</td>
<td>14/14</td>
<td>76 ± 41</td>
<td>K (100%), C, S, CP (each 45%)</td>
<td>Infections (total n = 62, severe n = 8)</td>
<td>Steroids (11), CYC (1), AZA (1), MMF (9), CQ (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mushiko 2013</td>
<td>10 (0)</td>
<td>SLEDAI, anti-dsDNA AB, anti-VRT-101</td>
<td>SLEDAI (n.s.)</td>
<td>All parameters (n.s.)</td>
<td>Not stated</td>
<td>2</td>
<td>Arthritis (80%), MC (60%) (infections, n = 2)</td>
<td>Steroids (n = 9), AZA (n = 7), MTX (n = 1), HCQ (n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The major clinical manifestations leading to the initiation of immunoadsorption are given.

**Long term follow-up data are presented. Assessment of a further decline between their initial report and the follow-up report indicated a non-significant change in anti-dsDNA antibodies.*
21.60% and 42.02 ± 22.14%, respectively [12]. Selesor® treatment in pregnant women with APS and previous miscarriage in 7/9 led to a decrease in antiphospholipid antibodies in 7/9, while lupus anticoagulant negativity and decrease in anticardiolipin antibodies was observed in 4 patients each [56–58]. Reduction of C1q by 29.4 ± 16.3% could be achieved following Immunosorba® treatment [47].

A method to adsorb disease specific antibodies was used by Hershko and colleagues. In a feasibility and safety study the use of Luposor® to eliminate anti-VRT-101 antibodies, which correlated with disease activity and demonstrated pathogenic properties, was tested. VRT-101 represents a target epitope located at the globular part of the α-chain of laminin. After a follow-up time of 8 weeks, anti-VRT-101 antibody decreased by 25% [53]. GM-CSF secreting PBMC were increased in active disease, whereas interferon-γ secreting cells were decreased. Moreover, in active disease an expansion of CD71+ (transferrin receptor) on CD4+ T-cells and CD86 on B-lymphocytes was observed. Treatment of Ig-Therasorb® led to a reduction of GM-CSF secreting PBMC and CD4+CD71+ T-cells, which correlated with the reduction of anti-dsDNA antibodies [11]. Following Ig-Therasorb® treatment, a normalisation of IL-10 secreting PBMC was observed [44] (Table 2 and Fig. 1).

3.2.2.4. Conclusion. High affinity IAS columns such as Ig-Therasorb®, Immunosorba® or Globaffin® are capable of removing disease-specific antibodies such as anti-dsDNA antibodies with one session. Total serum IgG declines by 75% [52]. Low affinity columns such as Selesor® or Immunosorba® have lesser degrees of efficacy. More specific columns such as Lupusor® remove disease-specific antibodies, whereas a lack of increase in complement C3/C4 was shown [53]. Normalisation of complement treated with other columns could be achieved in most patients, along with a decline in anti-dsDNA antibodies. Treatment with high affinity columns led to reductions of GM-CSF. IL-10 and CD4+CD71+ T-cells, while removal of the anaphylatoxins C3a and C4a could be demonstrated in patients undergoing treatment with low affinity IAS columns. A decline of anti-VRT-101 antibodies could be observed following Luposor® extracorporeal treatment.

3.3. Efficacy of plasma exchange in systemic lupus erythematosus and antiphospholipid syndrome

Comparison of different observational studies and randomised controlled trials is possible to a limited extent, since disease manifestations, processed plasma, outcome parameters, duration of follow-up and patient selection (i.e. refractory, 1st line treatment, APS and pregnancy outcome) showed a strong variation.

3.3.1. Plasma exchange as concomitant strategy in 1st line treatment

A multicentre survey by the LNSG revealed a decrease in serum creatinine from a mean value of 1.93 ± 1.9 to 1.56 ± 1.0 mg/dl after 9 months of follow-up. The number of patients undergoing maintenance haemodialysis decreased from 5 to 3 after initiation of PLEX. However, information about concomitant immunosuppression and the PLEX procedure and dosing are lacking [29]. Short-term PLEX defined as 4–11 sessions per patient with 80% of plasma processed combined with oral or pulsed steroids and CYC with an initial dosage of 3 mg/kg body weight and further adaption to white blood count achieved a favourable outcome in patients with lupus nephritis. Serum creatinine and proteinuria decreased from an initial value of 1.0–5.8 to 0.5–4.3 mg/dl and from a urinary protein excretion of 1.0–4.5 to 0.1–2.2 g/d after treatment initiation. Notably, proteinuria ≤ 200 mg/day was detected in eight undergoing sequential treatment. Information about follow-up time after initiation of treatment is missing [30]. Another randomised controlled trial evaluated the efficacy of combined treatment (PLEX 3 sessions with plasma processing of 50 ml/kg and CYC 750 mg/m²) to CYC (750 mg/m²) with a monthly repetition for at least 6 sessions (in the case of partial remission 3 further courses) and found a higher proportion of patients with ‘synchronised’ therapy in complete remission after 6 months. However, the favourable effect was lost in longer follow-up. At the time of last assessment, SLICC/ACR damage index was 2.9 in the ‘synchronised’ therapy group and 4 in the comparator group [33].

A comparison of either PLEX (36 session in 14 patients, 3 l per session) followed by 10 g intravenous immunoglobulin for three consecutive days combined with CYC (10–12 mg/kg body weight fortnightly for 4 pulses, then 4 further pulses monthly) and steroids in a tapering regimen to IAS with IMPH-350® in combination with CYC and steroids showed similar clinical efficacy as assessed by SLEDAI and similar relapse rates (3/14 patients in each group) after 6 months [35].

3.3.2. Plasma exchange in the context of relapsing disease

In an older report with variable PLEX dosing and frequency, a majority of patients with lupus nephritis (5/7) showed an improvement following PLEX, whereas the effect was limited in those without lupus nephritis (2/4 with improvement) [28]. A large randomised controlled trial to elucidate clinical efficacy of SOC (prednisolone at least 60 mg) in conjunction with PLEX (10–12 sessions, plasma processed at least 3 l per session) compared to SOC, observed no difference in clinical outcomes between groups. However, newly diagnosed patients were included in this trial. The number of patients achieving remission of renal disease defined as creatinine ≤ 1.2 mg/dl and a 24-hour urinary protein excretion of ≤ 0.2 g/d was 30% in the PLEX arm. 10 out of 40 patients in the PLEX arm progressed to end stage renal failure within 136 weeks of follow-up. During an extended follow-up, another four reached end stage renal failure [7].

3.3.3. Plasma exchange in refractory disease

Older observations in patients with refractory lupus nephritis and deteriorating kidney function revealed good efficacy in this setting, although benefits of concomitant therapy with prednisolone (60–80 mg) and CYC may have contributed. A total of 16–18 sessions were carried out with a plasma dose of 1100 to 2800 ml. An improvement in kidney function with a decline of serum creatinine from a pre-PLEX value of 2.1 ± 1.4 mg/dl to 1.2 ± 0.5 mg/dl after 11.5 months could be detected [29]. Wallace et al. investigated the efficacy of two different devices to perform PLEX with exchange of 40 ml/kg body weight and a total of 12 sessions within 4 weeks on refractory lupus nephritis. After a follow-up period of two years, the initial creatinine decreased from 2.27 ± 1.25 to 1.84 ± 1.62 mg/dl, while proteinuria dropped from a nephrotic range (6.06 g/d) to 2.75 ± 3.7 g/d. Despite the positive overall effects, three progressed to end stage renal disease [31].

A preliminary report by the LPSG investigating the role of ‘synchronised’ treatment with PLEX and subsequent CYC to hamper a compensatory ‘rebound’ effect of tissue adjacent ‘pathogenic clones’. ‘Synchronised’ treatment consisted of PLEX with a processed plasma volume of 60 ml/kg body weight (3 sessions), followed by 3 pulses CYC 12 mg/kg body weight, 3 pulses prednisolone à 2 mg/kg and subsequent oral CYC (start with 50 mg, increasing in steps to 100–250 mg) and oral prednisolone with complete withdrawal after 6 months. Treatment-free remission was achieved in 12 of 14 patients included with a mean SLAM of 3.3 (0–7) after 12 months. In general, disease activity as assessed by SLAM decreased from 28.4 to 8.9 [2–13] after six months. Eight patients followed for 6 years (52–97 months) after initiation did not experience a relapse and immunosuppression was not re-initiated. Among the other patients, three relapses occurred after 12–39 months and repetition of the initial protocol led to remission again [8,59].

A small randomised controlled trial comparing CYC (6 pulses 0.75–1.0 g/m² body surface area) or PLEX (average number 8.4, processed plasma 3 l per session) in combination with steroids in patients with lupus nephritis showed comparable clinical efficacy with respect to proteinuria (2.6 ± 0.8 to 0.8 ± 0.4 g/d in the CYC group and 2.7 ± 0.7 to 0.7 ± 0.4 g/d in the PLEX group) and serum creatinine [10]. Retrospective analysis of patients with steroid-resistant lupus nephritis either receiving PLEX/IAS (2 l processed, short-term and prolonged extracorporeal treatment), PLEX/IAS combined with CYC or CYC revealed highest remission

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and lowest relapse rates for the cohort receiving 'synchronised' therapy, although these alterations did not achieve significance [34].

Patients with refractory autoimmune thyroid disease due to underlying SLE experienced an improvement in thyroid stimulating hormone values regardless of the underlying autoimmune thyroid phenomenon. In common with this finding, a general improvement of SLEDAI could be observed, from an initial SLEDAI score of 23 ± 4 to 8 ± 3 after 12 months of follow-up. PLEX sessions were slowly tapered from an initial regimen of 2–3/week (3 l plasma processed). In patients with underlying lupus nephritis, proteinuria decreased from 2.93 ± 1.64 g/d to 0.72 ± 0.41 g/d after 12 months [39].

3.3.4. Plasma exchange in antiphospholipid syndrome, pregnancy and in the prevention of congenital atrioventricular heart block

Pregnant women with at least one previous pregnancy complication, either abortion, foetal death or live birth with death in neonatal intensive care, PLEX was performed 3–times weekly with 100% of plasma processed during each session, until lupus anticoagulant activity was suppressed and anti-cardiolipin antibodies were lowered. Withdrawal of PLEX was possible in most of the patients after 16–18 weeks of gestation with the exception of 3 patients with prolonged extracorporeal treatment (21–23 weeks) due to persistent antibody titres. All patients received concomitant prednisolone treatment at a dose of 10 mg/day. The live birth rate was 100%, with a reassuring complication rate consisting of mild pre-eclampsia (5.5%), foetal distress and oligohydramnios (16.66% each), pre-term delivery (22.2%) and thrombocytopenia (5.5%) [38] (Table 1). Ruffatti and colleagues reported on the outcome of anti-Ro/La-related congenital atrioventricular heart block following a combination therapy of weekly PLEX, fortnightly IVIg (1 g/kg) and daily betamethasone (4 mg/daily) throughout pregnancy, a combination therapy of weekly PLEX, fortnightly IVlg (1 g/kg) and daily betamethasone (4 mg/daily) throughout pregnancy, a combination therapy of weekly PLEX, fortnightly IVlg (1 g/kg) and daily betamethasone (4 mg/daily) throughout pregnancy.

3.3.5. Conclusion

Interpretation of these studies is limited due to their designs and small patient numbers, but evidence for a PLEX benefit is stronger in those with refractory severe disease and pregnancy or with APS and a history of pregnancy complications. Notable concerns are the impact of concomitant therapy on assessing PLEX benefit, of the differentiation between reversible and irreversible disease features, of the variability in dosing and PLEX procedure and the inclusion of new onset patients likely to initially respond well to standard therapy. PLEX may be a therapeutic option in those with refractory disease in the setting of nephritis, or central nervous system or haematological manifestations of SLE. In a small multicentre trial comparing PLEX in combination with steroids to cytotoxic drugs and steroids, Derksen and colleagues did not find a difference in terms of renal outcome. Thus, in the setting of a high risk of severe infections PLEX combined with steroids may be considered as a treatment option [9]. However, the optimal duration of PLEX has not been elucidated so far and has to be defined. Of note, replacement to maintain the oncostatic pressure is mandatory when plasma exchange is performed. Two possibilities of supplementation have emerged, namely 5% albumin and fresh frozen plasma. While the former has the advantage of viral inactivation, storage at room temperature, rarity of adverse events and iso-osmotic properties, the latter has more physiological properties with replacement of all plasma products, but bearing more disadvantages (risk of viral transmission, inconvenient storage, blood group compatibility, risk of allergic reactions and shortage of supply) [62].

3.4. Efficacy of immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome

In line with the limitations of PLEX studies, processed plasma, lupus manifestations and several different disease activity scores, duration of follow-up and patient selection (1st line, relapsing, refractory disease, and pregnancy outcome) differed. Moreover, different IAS columns with different physicochemical properties have been used in the treatment of SLE.

3.4.1. Immunoadsorption as concomitant strategy in 1st line treatment

Selesorb® treatment of newly diagnosed lupus nephritis patients with 2–4 sessions IAS (4 l plasma treated during each session) in combination with steroids revealed an improvement in proteinuria in all but one patient, and four of six patients showed normalisation of lymphocyte count during follow-up [44]. A subsequent open trial including 19 patients undergoing Selesorb® treatment in combination with steroids (mean number of 3.7 sessions, 4 l processed each) revealed a decline of SLEDAI from a baseline value of 10.2 to 4.5 after treatment. In addition, a steroid-sparing effect was proposed when compared to a historical group of patients with steroid monotherapy [63]. A small cohort of patients with lupus nephritis were treated with steroids, pulsed CYC and Immusorba® (4 times, 2 l processed per session). Proteinuria decreased from a baseline value of 2.2 ± 1.7 to 0.4 ± 0.6 g/d post-treatment and creatinine clearance increased [47]. Induction treatment with steroids, IVlg, pulsed CYC and Immusorba® (3 sessions, 3 l processed) achieved comparable results than the same induction treatment with additional PLEX. However, within three months of follow-up renal relapse occurred in three patients [35].

3.4.2. Immunoadsorption in the context of relapsing disease

Patients with disease relapse underwent IAS with a C1q column and had a total of 6 sessions. Serial disease activity assessment revealed an improvement in seven of eight patients. Disease activity assessed by ECLAM decreased from 7 [3–9] to 4 [1–6] and patient global assessment/visual analogue scale improved in every patient, from 42 (27–99) to 87 (52–98). Although kidney involvement was present in four, mean proteinuria in the whole cohort decreased from 0.83 (0.5–1.0) to 0.095 (0–3.0) following Mirio® treatment [54,55]. Willeke et al. reported on nine patients undergoing IAS treatment with Ig-Therasorb® (2–3 sessions, 4 l plasma processed each), while two patients received concomitant CYC and all were maintained on background immunosuppression. While the overall disease activity as assessed by SLAM decreased, two with moderate disease severity did not show any benefit and two with class IV lupus nephritis showed a therapeutic response in non-renal symptoms only [49]. Lupusorb® treatment (1 session, 2 l processed) was initiated in 10 with mild disease activity, whereas long term immunosuppression was continued. After 8 weeks, SLEDAI decreased by 21.15%, whereas urinary protein excretion increased by 37.14% from a baseline value of 0.35 g/d [53].

3.4.3. Immunoadsorption in refractory disease

Three sessions of IM-P® treatment (2 l plasma perfusion) in patients with refractory disease showed a good short-term response assessed three weeks after discontinuation of extracorporeal treatment [43]. Selesorb® treatment (4–6 sessions, 60 ml/kg plasma processed) in refractory patients with diverse predominant organ involvement led to clinical improvement in three, whereas one patient had worsening symptoms and one experienced no change [45]. Twenty patients inadequately controlled despite immunosuppressive treatment with steroids, azathioprine or cyclosporine were randomised to undergo either IMPH-350® or Ig-Therasorb® IAS. In both groups treatment was repeated after 1 month in case of limited or non-existent response following the first treatment session (three times, process of 2.5 l each). Treatment response was assessed by SLAM score decline of >30% from baseline and was achieved in 50% and 80% of patients in the IMPH-350® and...
lg-Therasorb® groups, respectively. SLAM scores decreased from 14.3 ± 5.6 to 9.4 ± 3.9 in the IMPH-350® and from 18.3 ± 5.5 to 9.2 ± 2.9 in the lg-Therasorb® group [48]. Eight patients with refractory disease underwent IAS with Immunosorba® (between four and 17 sessions, mean plasma processed 69 ± 30.4 l) and received concomitant CYC. During follow-up the SLAM score decreased from 23.8 ± 4.2 to 7.9 ± 4.3. In line with this, steroid dosage could be reduced subsequently, creatinine decreased from 2.3 ± 2.1 to 0.9 ± 0.2 mg/dl and urinary protein excretion improved in every patient [46]. Sixteen patients with severe lupus nephritis either refractory or with a contraindication to CYC were treated with lg-Therasorb® (gradual reduction of treatment sessions, 6–8 l plasma processed). Concomitant immunosuppression with CYC was switched to azathioprine or mycophenolate mofetil once clinical improvement was achieved. After 3 months, proteinuria reduced from 6.4 to 4.5 g/d (56% of patients reached a R50), creatinine clearance increased, and disease activity as assessed by SIS, SLEDAI and ECLAM decreased from 17 to 6, 21 to 6 and 8 to 3, respectively. Eleven patients entered an extended IAS programme. While proteinuria showed a decrease from 6.7 g/d at baseline to 2.9 g/d after one year, disease activity did not improve after 3 months. During the extended follow-up four major and minor flares were reported [50,51]. Long term follow-up of patients over 10 years revealed that patients not achieving remission after 1 year had a decline in protein- 

tent (5 to 31) with a total plasma seven had a history of miscarriage. The number of sessions was inconsis-

tent. Moreover, one patient developed squamous cell carcinoma and died [59]. In contrast, a non-severe allergic reaction was also reported in an observational study which was managed by a low-dose of steroids [49]. Stummvoll et al. observed three anaphylactic episodes in their patients. However, infections accounted for the majority of adverse events with four of them classified as severe infectious complications [50,51]. During long term follow-up a total of 62 infectious epis-

dodes were recorded, whereas eight of them were classified as severe [52]. Follow-up of patients who underwent Lupusorb® treatment exhibited several adverse events, whereas most of them were unrelated to IAS. However, two episodes of respiratory tract infections were re-

ported [53]. Loo et al. described thrombocytopaenia during follow-up. However, patients received concomitant CYC in this observational study [35]. A more profound decrease of immunoglobulins by 70–80% is generally achieved with lg-Therasorb® [51]. Following report of their initial publication, IAS columns were switched and Immunosorba® and Globaffin® columns were used throughout the observational period as well. Biesenbach et al. showed that each of them yielded a similar decrease in IgG and IgM decline following treatment with these high-affinity columns. Although there is no information available regarding re-

cover, normalisation of the respective immunoglobulin levels was achieved prior to the next treatment cycles [11].

3.6. Adverse event spectrum of immunoadsorption

A mild anaphylactic reaction was reported in the randomised controlled trial of Gaubitz and colleagues, who compared the efficacy of two different columns [48]. A non-severe allergic reaction was also re-
ported in an observational study which was managed by a low-dose of steroids [49]. Stummvoll et al. observed three anaphylactic episodes in their patients. However, infections accounted for the majority of adverse events with four of them classified as severe infectious complications [50,51]. During long term follow-up a total of 62 infectious epis-

dodes were recorded, whereas eight of them were classified as severe [52]. Follow-up of patients who underwent Lupusorb® treatment exhibited several adverse events, whereas most of them were unrelated to IAS. However, two episodes of respiratory tract infections were re-
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cover, normalisation of the respective immunoglobulin levels was achieved prior to the next treatment cycles [11].

3.4.4. Immunoadsorption in antiphospholipid syndrome and pregnancy

Among nine pregnant patients undergoing IAS with Selesorb®, seven had a history of miscarriage. The number of sessions was inconsis-
tent (5 to 31) with a total plasma flow of 1–1.5 l. In eight of the nine pa-

tients, live birth was achieved. Analysis of the placenta post-partum revealed infarction in 3 cases. During the pregnancy, no signs of active SLE were recorded [56] (Table 2).

3.4.5. Conclusion

Extracorporeal treatment with IAS has emerged as an alternative in the treatment of severe manifestations of SLE, especially in those pa-

tients refractory to conventional treatment options or with contraindi-
cation to standard treatments. Since this patient group has one of the most outstanding unmet needs, high-affinity IAS may be a valuable therapeutic option. In common with reports on PLEX efficacy, several differences are limiting general validity of these observations. In female pa-

tients with pregnancy a favourable outcome has been reported and this may be one important indication for IAS. The ideal duration of treat-

ment along with optimised plasma procession have yet to be defined.

3.5. Adverse event spectrum of plasma exchange

Early observational studies indicated a mortality rate of 9.4% out of 32 patients and 20% out of 10 patients undergoing PLEX. In the latter case, severe lupus activity along with development of opportunistic in-
fections accounted for the fatalities. In another observational study with a high cumulative CYC exposure as concomitant treatment, irreversible amenorrhea, haematologic changes, Herpes zoster virus infections were observed frequently. Moreover, one patient developed squamous cell carcinoma and died [59]. In contrast, an “interim-analysis” of the LPSG study revealed a high frequency of PLEX-related side effects, such as bleeding, puncture complications and catheter sepsis [8]. A more recent report indicated a good tolerability of treatment with steroids, CYC and PLEX. Persistent hypogammaglobulinaemia was observed in 33%, whereas both sustained amenorrhea and transient thrombocytopaenia were present in 25% [33]. The latter has been reported in further reports with local bleeding at the site of catheter insertion in two patients of the cohort published by Liu and colleagues [35,39]. Interestingly, no ana-
phylactic reactions have been described in these studies and complica-
tions of intensified treatment might be underestimated by these reports. In line with this assumption Aringer et al. observed six bacterial infections, four severe viral infections (including three cytomegalovirus infections) and one episode of Herpes zoster in nine patients undergoing ‘synchronised’ treatment. Notably, three patients died due to com-

plications of infections [64].

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This is surmounting the ability of sequential PLEX treatments. However, the decline in immunoglobulin levels below a threshold of 3 g/l may increase the risk of severe infections in patients with concomitant cytotoxic treatment and high dose steroids. This has to be addressed when treating patients with high-affinity IAS columns. No randomised controlled trials to provide evidence of efficacy and safety have been conducted so far.

Assessment of proteinuria in the short-term (<6 months) has been proven to be a suboptimal surrogate regarding renal activity, but reduction to a level below 0.8 g/d after 12 months of follow-up may be a predictor of long-term favourable renal outcome [67]. The general value of repeat renal biopsy in patients with refractory disease has to be addressed, since histological signs of treatment response may precede renal response and may be helpful in identifying patients who will benefit from intensified immunosuppression (e.g. addition of extracorporeal measures). Biomarkers may be in part helpful to guide treatment decisions, however since no concrete validated definition of refractoriness in SLE and lupus nephritis exist, this should be addressed in future prospective trials with appropriate sample collection. In terms of patient acceptance, extracorporeal treatment may not appear to be an elegant method to intensify treatment at first glance, since patients will need a central line inserted. However, short-term hospitalisation with a probability to have a lower frequency of clinic attendance may increase acceptance rate. Moreover and most importantly, counselling seems to be essential in this context and adherence to the current prescribed medication should be confirmed before intensification of immunosuppression.

The latter remains a problem in the management of patients with SLE [68]. In our opinion, global shortage and immunologic-mediated side effects of blood products may be a disadvantage of PLEX, favouring IAS as the preferential extracorporeal treatment form.

5. Conclusion

Patient selection is important to predict outcome after extracorporeal treatment. Treatment-naive SLE patients are generally responsible towards induction treatment and should not be commenced on IAS or PLEX. A small proportion of these patients may present with rapid progressive glomerulonephritis and the value of additional IAS or PLEX in this cohort has yet to be proven [69]. Moreover, the results in patients with relapsing disease forms are conflicting and other treatment options may be more valuable. A beneficial effect towards extracorporeal treatment forms has been reported following IAS or PLEX in those patients refractory to conventional immunosuppression and with risk of pregnancy complications. The value of both treatment forms in these patient cohorts with a high unmet need has to be proven in clinical trials. Above mentioned arguments would favour initiation of such a trial with IAS as extracorporeal treatment form.

Contribution statement

Conception and design: AK, BB, LFQ, DRWJ.
Analysis of the data: AK.
Drafting the article or revising it critically for important intellectual content: All authors.
Final approval of the version to be published: All authors.

Competing interests

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Take-home messages

- Plasma exchange and immunoadsorption are valuable treatment strategies in patients with refractory disease manifestations and in pregnancy.
- Immunoadsorption seems to have a favourable side effect spectrum compared to plasma exchange.
- There is a clear need to perform randomised controlled trials to evaluate efficacy, safety and tolerability of both treatment strategies in the treatment of systemic lupus erythematosus.

References


