Plasma Exchange and Immunoabsorption, one disease two strategies? 
Which to choose?

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Evidence Based Therapeutic Apheresis

- Harmful Substance
- Meaningful Depletion
- Clinical Benefit
Evidence Based Therapeutic Apheresis

Diseases are assigned to one of four categories:

1. TA is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment.

2. TA is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment.

3. The optimal role of TA is not established, and decision making should be individualized.

4. There is no evidence of benefit.

ASFA guidelines JCA 2013 special issue 6th edition
In addition to the strength of the indication, the risk/benefit assessment for TA must take account of the patient’s ability to tolerate the procedure.
GENERAL PRINCIPLES
Therapeutic Plasmapheresis

- Patient
  - separation
    - cells
    - Patient Plasma
      - Plasma substituted
Replacement fluid

- Saline solution
- Human albumin
- Fresh frozen plasma
- Hydroxyethyl starch
- Biseko® (plasma without Ig and coagulation factors)
Handling of plasma exchange fluid

n=190
Octaplas™

n=74
HA 5 – 8%
Octaplas™

n=17
HA 5 – 8%
TPE, how many times we should exchange the plasma volume?

$$y^o = \text{absolute initial concentration}$$

$$y^{\text{abs}} = \text{absolute final concentration}$$

$$y^\% = \text{relative final concentration} \ [\%]$$

$$e = \text{base of natural logarithms}$$

$$x = \text{number of times the patient’s total plasma volume is exchanged}$$

$$y^\% = e^{-x}$$

$$y^{\text{abs}} = y^o \times (100 - y^\%)$$

Every second day 1 TPE with 1, 1.5 or 2 PV treated

Recovery of IgG => 45% in 48 hours
Alteration in Blood Constituents by a 1-Plasma-Volume Exchange

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Percent Decrease from Baseline</th>
<th>Percent Recovery 48 Hours after Plasma Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting factors</td>
<td>25-50</td>
<td>80-100</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>63</td>
<td>~45</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>30-60</td>
<td>Variable</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>55-60</td>
<td>100</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>C₃</td>
<td>63</td>
<td>60-100</td>
</tr>
<tr>
<td>Platelets</td>
<td>25-30</td>
<td>75-100</td>
</tr>
</tbody>
</table>

*Replacement fluid consisting of 4% to 5% albumin in 0.9% sodium chloride.

*McLeod C. Bruce Apheresis Principles and Practice 2nd edition 2003*
## Target and Goals for TPE

<table>
<thead>
<tr>
<th>Substance to Remove</th>
<th>Treatment Volume (mL/kg)</th>
<th>Treatment Interval (in hours)</th>
<th>Treatment Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibodies</td>
<td>40-60</td>
<td>24-48</td>
<td>Four to six treatments</td>
</tr>
<tr>
<td>Immune complexes</td>
<td>40-60</td>
<td>24-48</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>40-60</td>
<td>24</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Cryoproteins</td>
<td>40-60</td>
<td>24-48</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Toxins</td>
<td>40-60</td>
<td>24-72</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura/Hemolytic uremic syndrome</td>
<td>40</td>
<td>24</td>
<td>Treat to establish remission</td>
</tr>
<tr>
<td>Immunologic rebound</td>
<td>40-60</td>
<td>24-48</td>
<td>Two to three treatments followed by immunosuppressive medication</td>
</tr>
</tbody>
</table>

*McLeod C. Bruce Apheresis Principles and Practice 2nd edition 2003*
Recommendation

• 1 to 2 times the Plasma volume

• Start with 2 to 3 procedures and than think about the interval if not given by treatment schedule
ATIII pre and post

TPE Octaplas

TPE HA 5-8%

TPE Octaplas + HA
Therapeutic Plasmapheresis

- Patient
  - primary separation
    - cells
    - Plasma plus Pathogen
      - Second separation
        - Plasma minus Pathogen
TECHNICAL ASPECTS IN IA
Immunadsorption with regenerative columns
Immunoadsorption
Ig removal – immunoadsorption

- Polyclonal sheep antibody
- Binding of IgG₁ – IgG₄, IgM, IgA, IgE, immune complexes

- 50 mL volume
- 10 treatments
- 2 months usage

- 100 mL volume
- ≥ 20 treatments
- 3 years usage
The Ig adsorbers bind all classes of the patient’s immunoglobulins
What is the optimal plasma loading per cycle?

- Loss of plasma in each cycle
- Overloading of adsorber without binding of antigen
### Immunoadsorption Prediction Software

**Patient Details:**
- Height: 95 cm
- Weight: 12 kg
- Age: 3 years
- Haematocrit: 30%
- Ig concentration: 5.00 g/l
- ACD:blood ratio: 1:22

**Cell Separator:** LIFE 18

**Adsorber:** Ig-flex

### Treatment Settings

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Plasma Speed</th>
<th>Loading Volume per Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>26 ml/min</td>
<td>150 ml</td>
</tr>
<tr>
<td>Treatment with optimal column loading</td>
<td>30 ml/min</td>
<td></td>
</tr>
<tr>
<td>Optimized</td>
<td>Maximal plasma speed</td>
<td>35 ml/min</td>
</tr>
</tbody>
</table>

**Change settings**

**Exit Application**

---

**Milenyi Biotec**
Prediction of processed Plasma Volume needed

Ig conc after %

Processed Plasma volume [ml]

11.5 % rest with 1350 ml treated => 1.6 x PV
Prediction of number of cycles needed => translation of PV in cycles of the system

Ig conc after %

Number of cycles performed

11.4 % rest with 9 cycles
Comparison of TPE and IA

1 liter human plasma protein (60 – 80g)

IgG (8 – 17 g)

Pathogen < 1g
Comparison of TPE and IA

Total Plasma Exchange

- Non-selective
- Loss of (essential) proteins
- Limited treatment volume
- A replacement fluid is needed
  - Risk of allergic reactions
  - (small) risk of infections from known and unknown pathogens

Immunoadsorption

- Selective
- No significant loss of (essential) proteins
- High treatment volumes possible
- No need of replacement fluids
„Apheresis Dose“

- **TPE**: 1 to 1.5 to 2 times the PV
- **IA**: 2 to 6 times the PV
- **Lipid-A**: 2 to 6 times the PV

Time axis
Target indications for TPE and IA

Ig antibodies
- IgE
  - Atopic dermatitis
  - Allergic asthma
  - Severe chronic urticaria
- Rheo Fibrinogen, CRP
  - Pulmonary hypertension
  - Diabetic Foot Syndrome
- LDL Lp(a)
  - Hypercholesterolemia
  - Pure Lp(a)
- LDL
- Plasma Exchange

IgE
- Atopic dermatitis
- Allergic asthma
- Severe chronic urticaria

Ig antibodies
- Hemolytic anemia
- Lupus erythematosus
- Sjögren's syndrome
- Systemic Sclerosis
- ITP/TTP
- HUS
- Wegener's granulomatosis
- Goodpasture's syndrome

Neurology
- Myasthenia gravis
- Guillain-Barré syndrome
- Lambert-Eaton syndrome
- Devic's syndrome
- Multiple sclerosis
- Encephalitis
- CIPD
- Sudden hearing loss
- Venous leg ulcer
- Raynaud's syndrome in SSc

Pulmonary Hypertension
- Pulmonary hypertension

Hemophilia

Solid Organ Transplantation
- Pemphigus

Pulmonary Hypertension
- Thrombangitis (Buerger's disease)

Hematology
- Hemophilia
- Hemolytic anemia

Surgery
- Kidney
- Heart
- Lung
- Liver
- Intestine

Cardiology
- Dilated Cardiomyopathy

Dermatology
- Diabetic Foot Syndrome

Neurology
- Peripheral Arterial Disease

Rheumatology
- Systemic Sclerosis
- Atopic dermatitis
- Hypercholesterolemia
Patient-adapted Software

Single-needle or double-needle mode

Switch between modes during treatment

Low blood flow at high target molecule concentration

<table>
<thead>
<tr>
<th>IgG g/l</th>
<th>Plasma ml/min</th>
<th>Blood ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>96</td>
</tr>
</tbody>
</table>
EXAMPLES FOR THE USE OF IA
Atopic Dermatitis: study Luebeck

• No response upon
  – Local steroids or calcineurin inhibitors for 4 weeks
  – UV therapy
  – Systemic steroids and calcineurin inhibitors for 8 weeks
IgE removal in atopic dermatitis

Patient 1

Source: University of Luebeck, Germany
Clinical outcome: SCORAD

Kasperkiewicz et al. 2010

SCORAD

before

week 5

week 13

mean 78.6 42.5 32.4
Skin bound IgE

Kasperkiewicz et al. 2010
Skin Histology

Week 1
(before IA)

Week 5
(after first IA cycle)

Week 13
(after second IA cycle)

Kasperkiewicz et al. 2010
2011: specific monoclonal IgE Adsorber

TheraSorb - IgE

- Eliminates up to 1 Million IU IgE per minute
- No elimination of IgG, IgM or IgA
Apheresis

1  2  3  4  5  6  7  8

Primary end point

weeks

Apheresis

1  2  3  4  5  6  7  8

weeks
Rheo adsorber

- Removal of fibrinogen, fibrin and c-reactive protein
- Reduction of blood and plasma viscosity
- Reduction of red cell aggregation
- Improvement of endothelial (dys-)function
Effect of **one** TheraSorb-Rheo treatment on patients with peripheral arterial disease (PAD Fontaine stage II – IV, n=10)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-apheresis</th>
<th>Post-apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total walking distance in meters</td>
<td>79 ± 60</td>
<td>Parameters</td>
</tr>
<tr>
<td>Pain-free walking distance in meters</td>
<td>60 ± 52</td>
<td>173 ± 76</td>
</tr>
</tbody>
</table>

ABO-incompatible transplantation with Glycosorb®-ABO

Glycosorb®-ABO specifically and effectively binds and removes blood group A and/or B antibodies
Specific Removal of Anti A and Anti B antibodies = No significant effect on coagulation factors

<table>
<thead>
<tr>
<th>Protein</th>
<th>A-column (n=2)</th>
<th>B-column (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>FVIII:C IU/ml</td>
<td>0.98</td>
<td>1.04</td>
</tr>
<tr>
<td>P-APTT (s)</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>P-PK (INR)</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>P-thromb. fact. 1+2 (nmol/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specific Removal of Anti A and Anti B antibodies
= No unspecific adsorption of proteins

<table>
<thead>
<tr>
<th>Protein</th>
<th>A-column (n=4)</th>
<th>B-column (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Alb (g/l)</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>9.1</td>
<td>8.9</td>
</tr>
<tr>
<td>IgA (g/l)</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>0.76</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Exclusive removal of anti-A and/or anti-B antibodies with Glycosorb®-ABO, makes it possible to treat several plasma volumes without saturation, leading to a more efficient titer reduction.
More efficient treatments:

- One Glycosorb®-ABO column can treat up to 15 L plasma per treatment session

- Two Glycosorb®-ABO columns connected in parallel can treat up to 30 L plasma per treatment session

= Fewer treatment sessions

Glycosorb®-ABO treatment can be performed simultaneously with hemodialysis
Original Article

ABO antibody and complement depletion by immunoadsorption combined with membrane filtration—a randomized, controlled, cross-over trial

Farsad Eskandary\textsuperscript{1}, Markus Wahrmann\textsuperscript{1}, Peter Biesenbach\textsuperscript{1}, Camilla Sandurkov\textsuperscript{1}, Franz König\textsuperscript{2}, Elisabeth Schwaiger\textsuperscript{1}, Thomas Perkman\textsuperscript{3}, Sarojinidevi König\textsuperscript{4}, Kurt Derfler\textsuperscript{1}, Gerhard J. Zlabinger\textsuperscript{4} and Georg A. Böhmig\textsuperscript{1}

\textsuperscript{1}Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria, \textsuperscript{2}Center for Medical Statistics, Informatics and Intelligent Systems, Section for Medical Statistics, Medical University Vienna, Vienna, Austria, \textsuperscript{3}Department of Laboratory Medicine, Medical University Vienna, Vienna, Austria and \textsuperscript{4}Institute of Immunology, Medical University Vienna, Vienna, Austria
**ABSTRACT**

**Background.** Potent antibody depletion techniques have paved the way to successful ABO-incompatible transplantation. Considering its efficiency regarding IgG removal, the use of non-antigen-specific semi-selective immunoadsorption (IA) has been advocated. One attractive strategy to overcome the caveat of incomplete IgM depletion and to interfere with complement activation could be the adjunctive use of membrane filtration (MF) to enhance the removal of macromolecules.

**Methods.** To investigate the depletion efficiency of semi-selective IA plus MF, we conducted a randomized, controlled, cross-over trial including patients on regular IA treatment for indications outside recipient desensitization. According to the results of sample size calculation, 14 subjects were enrolled. Two treatment sequences, a single session of IA plus MF followed by IA alone after ≥7 days (and vice versa), were analysed.

**Results.** IA plus MF markedly enhanced the median per cent reduction of ABO-specific IgM determined by flow cytometry (primary end point; 59 versus 23%, P < 0.001) and haemagglutination (2 versus 1 titre steps, P < 0.001), respectively. Combined treatment also substantially lowered C1q concentrations (86 versus 58% reduction, P < 0.001) and the functionality of classical complement as reflected by impaired in vitro C3 activation capability. IgG was strongly reduced without any additional effect of MF.

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**Conclusions.** We demonstrate that the innovative strategy of combining MF with semi-selective IA may substantially increase IgM elimination and affect classical complement activation. Our findings suggest that this new treatment concept could be an efficient strategy for recipient desensitization in ABO- and HLA-incompatible transplantation.

**Keywords:** ABO incompatibility, complement, immunoadsorption, immunoglobulins, randomized trial, transplantation

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**Trial flow chart.** Twenty potentially eligible patients were screened including flow cytometry to exclude patients with no detectable levels of ABO-specific IgM. IgM antibody-positive subjects were then assigned (stratification according to median MFI< versus >9000 for flow-cytometric ABO-specific IgM) to intervention groups AB (sequence: IA + MF/IA) or BA (sequence: IA/IA + MF), respectively.
**Figure 3:** Effect of apheresis on IgM reactivity. IgM and complement depletion by IA + MF in comparison to IA: (A) interpolated flow-cytometric ABO-specific IgM concentration (primary outcome parameter), (B) ABO-specific IgM titre assessed by direct agglutination, (C) total IgM concentration (nephelometry; normal reference value: 40–230 mg/dL), and (D) serum C1q level (radial immunodiffusion; normal reference value for C1q: range 5–20 mg/dL). Results are given as percent reduction from baseline levels or the reduction in titre steps from baseline titre, respectively. Provided are box plots showing median, IQR and range.
Kidney transplantation across HLA and ABO antibody barriers

Luis E. Becker\textsuperscript{a}, Caner Süsal\textsuperscript{b}, and Christian Morath\textsuperscript{a}

Purpose of review
A significant number of kidney transplantations in industrialized countries is currently performed over human leukocyte antigen (HLA) or ABO antibody barriers after living donation to encounter the increasing shortage of organs from deceased donors. Although patients with moderate titers of anti-A/B antibodies may easily be desensitized with no negative impact on allograft survival, recipients with high titers and HLA-sensitized patients demonstrate a substantial risk for antibody-mediated rejection, limiting long-term outcomes.

Recent findings
The use of powerful desensitization strategies including plasmapheresis and immunoabsorption, extended therapeutic options such as the application of the recently introduced complement inhibitors, and refined antibody detection techniques may further facilitate transplantations, especially in the HLA-sensitized kidney transplant recipient. On the contrary, special strategies such as the Eurotransplant Acceptable Mismatch Program or kidney paired exchange help improving long-term outcomes in these difficult to transplant patients by circumventing the HLA (or ABO) antibody barrier.

Summary
As compared with waiting for a compatible deceased donor organ, HLA- and ABO-incompatible transplantations performed in experienced centers have become a reasonable alternative for end-stage kidney disease patients with an incompatible live donor. Whenever possible, however, the transplantation should be performed between ABO-compatible donor-recipient pairs in the absence of positive crossmatch results.

Keywords
ABO-incompatible transplantation, crossmatch-positive transplantation, desensitization, donor-specific human leukocyte antigen antibodies
Whenever possible, transplantation across the HLA antibody barrier should be avoided.

In the absence of a compatible live donor, however, living donor kidney transplantation across the HLA antibody barrier may reduce waiting times with a dramatic impact on patient survival.

Transplantation over the ABO antibody barrier is now considered well tolerated with similar graft survival rates as ABO-compatible transplantations.

Powerful desensitization with, for example, immunoadsorption, new complement therapeutics and an increased knowledge on HLA and ABO antibodies may improve outcomes in the near future.

Special programs such as the Eurotransplant Acceptable Mismatch Program or kidney paired exchange can help avoiding HLA and ABO antibody barriers.
FIGURE 1. Overview of desensitization protocols for the living donor kidney transplantation across HLA and ABO antibody barriers. (a) Scheme for a standard desensitization protocol performed by the majority of centers with modifications in the utilization of desensitization devices, and (b) Desensitization protocol for HLA (blue) and ABO (red) incompatible living donor kidney transplantation at the University of Heidelberg [9*,20,21]. Anti-CD20 therapy is usually performed with rituximab 375 mg/m², anti-IL-2R therapy with basiliximab 20 mg and anti-C5 therapy with eculizumab 600–1200 mg Ab: Anti-A, Anti-B or donor-specific antibodies. ATG: antithymocyte globulin. IA: immunoabsorption. XM: crossmatch.
<table>
<thead>
<tr>
<th>First author</th>
<th>Number of patients</th>
<th>Transplant period</th>
<th>XM/DSA positivity</th>
<th>Desensitization method</th>
<th>Donor type</th>
<th>Follow-up (months)</th>
<th>Graft survival (%)</th>
<th>AMR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thielke et al. [29]</td>
<td>51</td>
<td>2001–2007</td>
<td>FCXM</td>
<td>PP + low dose IVIg</td>
<td>LDK</td>
<td>12</td>
<td>93</td>
<td>24</td>
</tr>
<tr>
<td>Haririan et al. [17]</td>
<td>41</td>
<td>1999–2006</td>
<td>FCXM</td>
<td>PP + low dose IVIg</td>
<td>LDK</td>
<td>12</td>
<td>89.9</td>
<td>12 (up to day 10 only)</td>
</tr>
<tr>
<td>Bartel et al. [27]</td>
<td>68</td>
<td>1999–2008</td>
<td>PRA &gt;40%; CDC (N=21); DSA (N=30)</td>
<td>IA</td>
<td>DDK</td>
<td>60</td>
<td>63</td>
<td>24–30</td>
</tr>
<tr>
<td>Morath et al. [21]</td>
<td>34</td>
<td>2006–2009</td>
<td>CDC and/or ELISA (N=17); DSA (N=10)</td>
<td>IA + anti-CD20 (LDK); PP + anti-CD20 (DDK)</td>
<td>LDK (N=6); DDK (N=28)</td>
<td>12</td>
<td>100 (LDK); 92.4 (DDK)</td>
<td>9</td>
</tr>
<tr>
<td>Stegall et al. [30**]</td>
<td>26</td>
<td>2008–2010</td>
<td>FCXM</td>
<td>(PP) + anti-C5 antibody</td>
<td>LDK</td>
<td>12 (mean)</td>
<td>100</td>
<td>8 at 3 months</td>
</tr>
<tr>
<td>Montgomery et al. [19**]</td>
<td>211</td>
<td>1998–2009</td>
<td>CDC (N=74); FCXM (N=95); DSA (N=42)</td>
<td>PP + low dose IVIg</td>
<td>LDK</td>
<td>12</td>
<td>n.a. (patient survival 90.6)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Morath [28]</td>
<td>10</td>
<td>2007–2010</td>
<td>CDC (N=9); DSA (N=1)</td>
<td>IA + anti-CD20</td>
<td>LDK</td>
<td>24</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Klein et al. [26]</td>
<td>23</td>
<td>2007–2012</td>
<td>CDC (N=11); ELISA (N=1); DSA (N=11)</td>
<td>IA + anti-CD20 (N=19); PP + anti-CD20 (N=4)</td>
<td>LDK</td>
<td>24</td>
<td>100</td>
<td>22</td>
</tr>
<tr>
<td>Vo et al. [10]</td>
<td>207</td>
<td>2006–2011</td>
<td>PRA &gt;80%; CDC; FCXM</td>
<td>high dose IVIg + anti-CD20</td>
<td>LDK (N=56); DDK (N=151)</td>
<td>48</td>
<td>87.5</td>
<td>22</td>
</tr>
<tr>
<td>Bentall et al. [18*]</td>
<td>102</td>
<td>2000–2006</td>
<td>FCXM</td>
<td>PP + low dose IVIg + Spx (N=16); PP + high dose IVIg (N=48); high dose IVIg (N=21); No desensitization (N=17)</td>
<td>LDK</td>
<td>60</td>
<td>70.7 (death-censored)</td>
<td>37.2</td>
</tr>
</tbody>
</table>

AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; DDK, deceased donor kidney; DSA, donor-specific antibody; FCXM, flow cytometry crossmatch; IA, immunoadsorption; IVIg, intravenous immunoglobulins; LDK, living donor kidney; n.a., not applicable; PP, plasmapheresis; PRA, pan-reactive antibody; Spx, splenectomy; XM, crossmatch. Modified from [20].
<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>Number of patients</th>
<th>Transplant period</th>
<th>Desensitization method</th>
<th>Successful desensitization (%)</th>
<th>Follow-up (months)</th>
<th>Graft survival (%)</th>
<th>AMR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montgomery et al. [7]</td>
<td>60</td>
<td>1999–2007</td>
<td>PP + low dose IVlg + Spx (N = n.a.) or anti-CD20 (N = n.a.)</td>
<td>98.4</td>
<td>12</td>
<td>98.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Genberg et al. [12]</td>
<td>43</td>
<td>2001–2010</td>
<td>Antigen-specific IA + low dose IVlg + anti-CD20</td>
<td>95.6</td>
<td>4.5 (mean)</td>
<td>91</td>
<td>4.7</td>
</tr>
<tr>
<td>Flint et al. [13]</td>
<td>37</td>
<td>2005–2008</td>
<td>PP + low dose IVlg</td>
<td>n.a.</td>
<td>26 (median)</td>
<td>100</td>
<td>5.4</td>
</tr>
<tr>
<td>Fuchinoue et al. [8]</td>
<td>113</td>
<td>2002–2008</td>
<td>Double filtration PP + Spx (N = 63) or anti-CD20 (N = 50)</td>
<td>n.a.</td>
<td>12</td>
<td>Spx: 96.8</td>
<td>Spx: 15.9</td>
</tr>
<tr>
<td>Biglarnia et al. [33]</td>
<td>19</td>
<td>2004–2008</td>
<td>Antigen-specific IA + low dose IVlg + anti-CD20</td>
<td>n.a.</td>
<td>40 (median)</td>
<td>100</td>
<td>5.3</td>
</tr>
<tr>
<td>Morath et al. [9*]</td>
<td>12</td>
<td>2005–2010</td>
<td>Nonantigen-specific IA + anti-CD20</td>
<td>100</td>
<td>18</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

AMR, antibody-mediated rejection; IA, immunoadsorption; IVlg, intravenous immunoglobulins; n.a., not applicable; PP, plasmapheresis; Spx, splenectomy.
<table>
<thead>
<tr>
<th>Table 3. The Heidelberg algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pretransplant identification of high-risk sensitized patients</strong></td>
</tr>
<tr>
<td>CDC-PRA with DTT $\geq 85%$ (current or historical)</td>
</tr>
<tr>
<td>HLA class I and II antibody positivity in ELISA screening</td>
</tr>
<tr>
<td>HLA class I positivity in ELISA screening at retransplantation</td>
</tr>
<tr>
<td><strong>Donor-dependent</strong></td>
</tr>
<tr>
<td>Positive CDC B-cell XM in retransplant recipients with HLA antibody positivity in ELISA screening</td>
</tr>
<tr>
<td>Positive CDC T-cell XM</td>
</tr>
<tr>
<td>DSA with more than 1000 MFI in luminex testing (LDK)</td>
</tr>
<tr>
<td><strong>Good HLA match in patients with HLA class I and class II antibody positivity in ELISA screening (DDK)</strong></td>
</tr>
<tr>
<td>If CDC-PRA with DTT $&lt; 10%$: 0–2 HLA-A, HLA-B, HLA-DR mismatches</td>
</tr>
<tr>
<td><strong>Eurotransplant Acceptable Mismatch Program (DDK)</strong></td>
</tr>
<tr>
<td><strong>Pretransplant desensitization</strong></td>
</tr>
<tr>
<td>Repeated immunoabsorption treatments (LDK)</td>
</tr>
<tr>
<td>Rituximab 375 mg/m$^2$ (when all crossmatches are negative)</td>
</tr>
<tr>
<td><strong>Posttransplant treatment (until stable graft function is achieved, e.g. SCr &lt;2 mg/dl)</strong></td>
</tr>
<tr>
<td>Repeated immunoabsorption treatments (LDK)</td>
</tr>
<tr>
<td>On days 7 and 90 after transplantation</td>
</tr>
<tr>
<td><strong>Protocol biopsies</strong></td>
</tr>
<tr>
<td><strong>Posttransplant monitoring of donor-specific antibodies</strong></td>
</tr>
</tbody>
</table>

CDC, complement-dependent cytotoxicity; DDK, deceased donor kidney; DSA, donor-specific antibody; DTT, dithiothreitol; LDK, living donor kidney; PRA, panel-reactive antibody; SCr, serum creatinine; Spx, splenectomy; XM, crossmatch. Modified from [21].
Therapeutic Apheresis in Kidney Transplantation: A Review of Renal Transplant Immunobiology and Current Interventions With Apheresis Medicine

Angie Nishio-Lucar,¹ Rasheed A. Balogun,¹* and Scott Sanoff²

¹Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia
²Division of Nephrology, Duke University School of Medicine, Durham, North Carolina

Transplantation is the treatment of choice for end stage renal disease. Kidney transplants convey both a significant survival advantage to the individual recipient as well as cost savings to the medical system. Circulating alloantibodies directed against donor human leukocyte antigens and blood group antigens are fairly common among potential recipients. They are known to injure allografts, shorten allograft survival, and limit access to kidney transplantation. Hence, screening for pretransplant alloantibodies using complement dependent cytotoxic cross-matching and more sensitive techniques such as the solid phase assays, have become routine in an attempt to avoid incompatible donor-recipient pairs and risk stratify those with donor specific antibodies (DSA). By removing harmful antibodies, therapeutic apheresis (TA) has become a critical tool for improving access to transplantation in cases where the immunologic risk had previously been considered unacceptable. It has also allowed us to transplant across the barrier of ABO blood group incompatibility and expand the pool of donors with reasonable success. Furthermore, it is an important tool in the treatment of antibody-mediated rejection. Advanced apheresis technologies, such as immunoadsorption, and the use of TA in combination with innovative paired-donor exchange programs, offer the potential to further improve access and outcomes, minimizing the shortcomings of one single form of therapy alone. J. Clin. Apher. 28:56–63, 2013. © 2013 Wiley Periodicals, Inc.

Key words: antibody; apheresis; outcome; desensitization

Ruocco E, Wolf R, Ruocco V, Brunetti G, Romano F, Lo Schiavo A.

Abstract
Pemphigus, a prototypical organ-specific human autoimmune disease, may be associated with other immunity-related disorders, viral infections, and different types of tumors. Coexistence with immune diseases is fairly frequent and, for some of them (eg, myasthenia gravis, Basedow's disease, rheumatoid arthritis, or lupus erythematosus), common pathogenic mechanisms can be considered. The association with viral infections (mainly herpesvirus infections) raises the question of whether the virus triggers the outbreak of the disease or simply complicates its clinical course. Neoplastic proliferations coexisting with pemphigus have a different histogenesis and the pathologic link may vary according to the associated tumor (thymoma, lymphoma, carcinoma, or sarcoma). A subset of pemphigus-neoplasia association is represented by Anhalt's paraneoplastic pemphigus, with peculiar clinical, histologic, and immunologic features characterizing it. Coexistence of pemphigus with Kaposi's sarcoma, albeit not frequent, offers an intriguing speculative interest. The cornerstone of management in pemphigus is the combination of systemic corticosteroids and immunosuppressants. The conventional treatment used in most cases is based on oral administration of deflazacort and azathioprine. In selected cases, mycophenolate mofetil is preferred to azathioprine. Severe forms of pemphigus require intravenous pulse therapy with dexamethasone (or methylprednisolone) and cyclophosphamide. In the recent years, the use of high-dose intravenous immunoglobulin therapy has gained several consents. Rituximab, a monoclonal anti-CD 20 antibody, which affects both the humoral and cell-mediated responses, has proved to give a good clinical response, often paralleled by decrease of pathogenic autoantibodies. The combination with intravenous immunoglobulin offers the double advantage of better clinical results and a reduced incidence of infection. Interventional treatments, such as plasmapheresis and extracorporeal immunoadsorption, are aimed at patients with life-threatening forms of pemphigus and high levels of circulating autoantibodies, a circumstance where the medical therapy alone risks failing. Second-line treatments include gold salts (which we do not favor because of the acantholytic potential inherent in thiol structure) and the association of oral tetracyclines with nicotinamide, which is rather safe. Local treatments, supplementary to the systemic therapy, are aimed at preventing infections and stimulating reepithelialization of eroded areas. Innovative topical treatments are epidermal growth factor, nicotinamide gel, pimecrolimus, and a proteomics-derived desmoglein peptide. Pemphigus patients should be warned against over-indulging in unnecessary drug intake, prolonged exposure to ultraviolet rays, intense emotional stress, and too spiced or too hot foods. Cigarette smoking is not contraindicated in pemphigus patients because of the nicotine anti-acantholytic properties. Copyright © 2013. Published by Elsevier Inc.
Targeting anti-beta-1-adrenergic receptor antibodies for dilated cardiomyopathy

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Anti-beta-1-adrenergic receptor antibodies (anti-β1AR Abs) have long been implicated in the pathogenesis of dilated cardiomyopathy (DCM). It is believed that these autoantibodies bind to and constitutively stimulate the β1AR to promote pathological cardiac remodelling and β1AR desensitization and downregulation. The prevalence of anti-β1AR Abs in patients with DCM ranges from 26% to 60%, and the presence of these autoantibodies correlates with a poor prognosis. Several small studies have shown improvements in functional status, haemodynamics, and biomarkers of heart failure upon removal or neutralization of these antibodies from the sera of affected patients. Traditionally, removal of anti-β1AR Abs required immunoabsorption therapy with apheresis columns directed against human immunoglobulins (Igs) and subsequent i.v. Ig infusion, thereby essentially performing a plasma exchange transfusion. However, recent advances have allowed the development of small peptides and nucleotide sequences that specifically target and neutralize anti-β1AR Abs, providing a hopeful avenue for future drug development to treat DCM. Herein, we briefly review the clinical literature of therapy directed against anti-β1AR Abs and highlight the opportunity for further research and development in this area.
### Table 1 Human studies of non-selective immunoabsorption of anti-beta-1-adrenergic receptor antibodies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallukat et al. (1996)</td>
<td>Non-selective IA; Ig substitution</td>
<td>Case series (n = 8)</td>
<td>NR</td>
<td>7/8 patients improved NYHA class</td>
</tr>
<tr>
<td>Dorffel et al. (1997)</td>
<td>Non-selective IA; Ig substitution</td>
<td>Case series (n = 9)</td>
<td>6 days</td>
<td>Improved haemodynamics; no change in LVEF</td>
</tr>
<tr>
<td>Muller et al. (2000)</td>
<td>Non-selective IA</td>
<td>Prospective case-control (n = 34)</td>
<td>1 year</td>
<td>5/9 patients alive; improved LVEF in survivors</td>
</tr>
<tr>
<td>Felix et al. (2000)</td>
<td>Non-selective IA; Ig substitution</td>
<td>Randomized control trial (n = 18)</td>
<td>3 months</td>
<td>Improved LVEF and NYHA class</td>
</tr>
<tr>
<td>Felix et al. (2002)</td>
<td>Non-selective IA; Ig substitution</td>
<td>Case series (n = 11)</td>
<td>3 days</td>
<td>Improved haemodynamics</td>
</tr>
<tr>
<td>Staudt et al. (2002)</td>
<td>Non-selective IA vs. IA with low affinity for IgG3 (enrich IgG3)</td>
<td>Case control (n = 18)</td>
<td>3 months</td>
<td>Improved LVEF, NYHA class, and CI in patients with reduced IgG3 levels</td>
</tr>
<tr>
<td>Mobini et al. (2003)</td>
<td>Non-selective IA; Ig substitution</td>
<td>Case control (n = 22)</td>
<td>3 months</td>
<td>Improved LVEF and CI, regardless of anti-beta-1AR Ab status</td>
</tr>
<tr>
<td>Knebel et al. (2004)</td>
<td>Non-selective IA with Ig substitution vs. no IA</td>
<td>Retrospective case-control (n = 34)</td>
<td>3 years</td>
<td>Decreased hospitalized days; improved NYHA class</td>
</tr>
<tr>
<td>Yoshikawa et al. (2009)</td>
<td>Non-selective IA</td>
<td>Case series (n = 10)</td>
<td>NR</td>
<td>Reduced BNP</td>
</tr>
<tr>
<td>Dandel et al. (2012)</td>
<td>Non-selective and selective IA</td>
<td>Retrospective case series (n = 108)</td>
<td>5.3 – 14.7 years</td>
<td>Improved LVEF and transplant/VAD-free survival if baseline anti-beta-1AR Abs present</td>
</tr>
</tbody>
</table>

Ab, antibody; β1AR, beta-1-adrenergic receptor; CI, cardiac index; IA, immunoabsorption; Ig, immunoglobulin; NR, not reported; VAD, ventricular assist device.

### Table 2 Human studies of selective immunoabsorption of anti-beta-1-adrenergic receptor antibodies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staudt et al. (2005)</td>
<td>Selective IgG3 IA</td>
<td>Case-control (n = 18)</td>
<td>3 months</td>
<td>Improved if effective IgG3 reduction</td>
</tr>
<tr>
<td>Staudt et al. (2006)</td>
<td>Selective IgG3 IA; Ig substitution</td>
<td>Randomized trial (n = 22)</td>
<td>6 months</td>
<td>Improved LVEF and CI in both groups, but no additional benefit with increased IA sessions</td>
</tr>
<tr>
<td>Staudt et al. (2006)</td>
<td>Selective IgG3 IA and Ig substitution vs. no IA</td>
<td>Case-control (n = 30)</td>
<td>3 months</td>
<td>Improved LVEF and NT-proBNP</td>
</tr>
<tr>
<td>Baba et al. (2010)</td>
<td>Selective IgG3 IA</td>
<td>Case series (n = 18)</td>
<td>3 months</td>
<td>Improved LVEF, 6 min walk, and BNP values in subjects with removal of anti-beta-1AR Abs and all other cardiodepressant Abs</td>
</tr>
<tr>
<td>Staudt et al. (2010)</td>
<td>Selective IgG3 IA; Ig substitution</td>
<td>Case series (n = 103)</td>
<td>6 months</td>
<td>Improved LVEF and NYHA class</td>
</tr>
<tr>
<td>Herda et al. (2010)</td>
<td>Selective IgG3 IA and Ig substitution vs. no IA</td>
<td>Case-control (n = 60)</td>
<td>3 months</td>
<td>Improved LVEF and exercise tolerance if anti-beta-1AR Abs were present at baseline</td>
</tr>
<tr>
<td>Wallukat et al. (2002)</td>
<td>IA with peptide mimicking anti-beta-1AR Ab epitope</td>
<td>Case series (n = 8)</td>
<td>1 year</td>
<td>Improved LVEF</td>
</tr>
<tr>
<td>Schimke et al. (2005)</td>
<td>IA with peptide mimicking anti-beta-1AR Ab epitope</td>
<td>Case series (n = 8)</td>
<td>1 year</td>
<td>Improved LVEF; decreased markers for oxidative stress</td>
</tr>
</tbody>
</table>

Ab, antibody; β1AR, beta-1-adrenergic receptor; CI, cardiac index; IA, immunoabsorption; Ig, immunoglobulin; NR, not reported; VAD, ventricular assist device.
The role of autoimmunity in thromboangiitis obliterans (Buerger’s disease)

Siva S. Ketha and Leslie T. Cooper
Gonda Vascular Center, Mayo Clinic and Foundation, Rochester, Minnesota

Address for correspondence: Leslie T. Cooper Jr., M.D. Division of Cardiovascular Diseases Mayo Clinic, 200 First Street SW. Rochester, MN 55905. cooper.leslie@mayo.edu

Thromboangiitis obliterans (TAO), or Buerger’s disease, is a nonatherosclerotic segmental vasculitis that affects the small- and medium-sized arteries and veins of the extremities and is strongly associated with tobacco exposure. The immunopathogenesis of TAO remains largely unknown. In the acute phase of the disease, macrophages and occasional giant cells are observed in the characteristic intraluminal thrombus with a relatively mild infiltration of CD4+ and CD8+ T cells and macrophages in the internal lamina. VCAM-1, ICAM-1, and E-selectin expression on the surface of vascular endothelial cells is increased. A variety of circulating autoreactive antibodies targeting endothelial cells and vessel wall components are associated with active disease. One recent report suggests that removal of circulating antibodies by immunoabsorption may decrease disease severity. TAO has been associated positively and negatively with various MHC class I and 2 genes; however, genetic testing is not currently used for clinical diagnosis or management. The possible links between tobacco exposure and loss of tolerance for vascular tissues, current management strategy for patients with TAO, and opportunities for translational science are discussed.

Keywords: Buerger’s disease, peripheral arterial disease, thromboangiitis obliterans
Tobacco (primary environmental trigger)

Injury to blood vessel in genetically susceptible individuals

Damaged endothelial cells

Increased expression of VCAM-1, ICAM-1, E-selectin on endothelial cell surface

Activated dendritic cells and macrophages leading to antiendothelial cell antibodies and autoreactive T cells

Innate and adaptive immune response

Highly cellular intraluminal thrombus

Intraluminal thrombus with polymorphonuclear leukocytes, mononuclear cells, multinucleated giant cells
Baumann et al. studied 10 TAO patients with chronic ischemic rest pain and evidence of ischemic lesions despite medical therapy. All the study subjects underwent IA over five consecutive days. All patients experienced a significant improvement in pain immediately after the treatment and remained pain free at one- and six-month intervals. There was also a significant increase in the maximum walking distance, transcutaneous oxygen tension, transcutaneous carbon dioxide tension, and photoplethysmography measurements after IA at one- and six-month intervals. These data support the theory that autoreactive antibodies are central to the pathogenesis of TAO.

Therapeutic Apheresis in Kidney Transplantation: A Review of Renal Transplant Immunobiology and Current Interventions With Apheresis Medicine

Angie Nishio-Lucar,¹ Rasheed A. Balogun,¹* and Scott Sanoff²

¹Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia
²Division of Nephrology, Duke University School of Medicine, Durham, North Carolina

Transplantation is the treatment of choice for end stage renal disease. Kidney transplants convey both a significant survival advantage to the individual recipient as well as cost savings to the medical system. Circulating alloantibodies directed against donor human leukocyte antigens and blood group antigens are fairly common among potential recipients. They are known to injure allografts, shorten allograft survival, and limit access to kidney transplantation. Hence, screening for pretransplant alloantibodies using complement dependent cytotoxic cross-matching and more sensitive techniques such as the solid phase assays, have become routine in an attempt to avoid incompatible donor–recipient pairs and risk stratify those with donor specific antibodies (DSA). By removing harmful antibodies, therapeutic apheresis (TA) has become a critical tool for improving access to transplantation in cases where the immunologic risk had previously been considered unacceptable. It has also allowed us to transplant across the barrier of ABO blood group incompatibility and expand the pool of donors with reasonable success. Furthermore, it is an important tool in the treatment of antibody-mediated rejection. Advanced apheresis technologies, such as immunoadsorption, and the use of TA in combination with innovative paired-donor exchange programs, offer the potential to further improve access and outcomes, minimizing the shortcomings of one single form of therapy alone. J. Clin. Apheresis 28:56–63, 2013. © 2013 Wiley Periodicals, Inc.

Key words: antibody; apheresis; outcome; desensitization

Effect of IgG immunoadsorption on serum cytokines in MG and LEMS patients
Fulvio Baggi, Federica Ubiali, Sara Nava, Valeria Nessi, Francesca Andreetta, Andrea Rigamonti, Lorenzo Maggi, Renato Mantegazza, Carlo Antozzi
Journal of Neuroimmunology Volumes 201–202, 15 September 2008, Pages 104–110

Abstract
We investigated the effect of IgG immunoadsorption (IA) on cytokine network in patients with treatment-resistant Myasthenia Gravis (MG) and Lambert–Eaton Syndrome (LEMS). We observed upregulation of interleukin (IL)-10, an anti-inflammatory and B cells growth factor, and reduction of pro-inflammatory factors such as IL-18 and IL-17, in both MG and LEMS after IA. Our observation suggests that the massive removal of antibodies might induce modifications of the cytokine balance linked to T and B cells mediated autoimmunity.
LEMS

IL-10

pg/ml

Pre IA  Post IA

IL-18

pg/ml

Pre IA  Post IA

IL-17

pg/ml

Pre IA  Post IA

TGF-β

ng/ml

Pre IA  Post IA
Abstract
Distinct connective tissue diseases (CTD's) such as systemic lupus erythematosus (SLE), systemic sclerosis, mixed connective tissue disease as well as dermato- and polymyositis comprise a group of diseases, where autoantibodies are not merely indicators of autoimmune disease, but also play an relevant role in the underlying pathogenicity. This knowledge led to the development of antibody targeting therapies using rituximab or belimumab. Upon this, therapeutic plasma exchange, and more recently immunoadsorption (IAS) have been successfully applied to remove pathogenic autoantibodies under various conditions in some of these CTD's. While the technique of IAS is superior to plasma exchange in regard to specificity and efficacy, the clinical use of IAS in CTD's is currently restricted to a small proportion of clinical situations with either refractory disease or the necessity to avoid aggressive immunosuppressive regimens. Despite the presence of a large number of case series and few controlled trials using IAS, there is a need for further prospective randomized trials to clearly define the role of IAS in these CTD's.
Antibodies with direct pathogenicity in SLE.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Directly linked to</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC, platelets</td>
<td>Hemolytic anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Anti-CD3</td>
<td>Reduced IL-2 production</td>
</tr>
<tr>
<td>Anti-T-cell receptor</td>
<td></td>
</tr>
<tr>
<td>Anti-Ro</td>
<td>Altered myocyte function, neonatal lupus, congenital heart block</td>
</tr>
<tr>
<td>Anti-N-methyl-D-aspartate receptors (NMDARs)</td>
<td></td>
</tr>
<tr>
<td>Anti-phospholipids</td>
<td>Thrombotic events, fetal loss</td>
</tr>
<tr>
<td>Anti-(\beta)2-glycoprotein 1</td>
<td></td>
</tr>
<tr>
<td>Anti-(\alpha)-actinin</td>
<td>Inflammatory response to mesangial cells</td>
</tr>
<tr>
<td>Anti-lipoprotein</td>
<td>Atherosclerosis-related events</td>
</tr>
</tbody>
</table>
## Autoantibodies and their link to organ involvement in SSc.

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scl-70 (topoisomerase-1)</td>
<td>Lung fibrosis</td>
</tr>
<tr>
<td>RNA polymerase III</td>
<td>Skin, pulmonary hypertension, renal involvement</td>
</tr>
<tr>
<td>U3RNP (fibrillarin)</td>
<td>Pulmonary hypertension, muscles</td>
</tr>
<tr>
<td>PM-Scl</td>
<td>Muscles</td>
</tr>
<tr>
<td>U1RNP</td>
<td>Muscles</td>
</tr>
<tr>
<td>Centromere</td>
<td>Pulmonary hypertension, esophageal disease</td>
</tr>
<tr>
<td>Th/To</td>
<td>Pulmonary hypertension and fibrosis, small bowel</td>
</tr>
<tr>
<td>U11/U12</td>
<td>Lung fibrosis</td>
</tr>
<tr>
<td>Ku</td>
<td>Muscle and joint involvement</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Vasculopathy</td>
</tr>
<tr>
<td>Angiotensin-II receptor type 1</td>
<td>Vasculopathy</td>
</tr>
</tbody>
</table>
Two sessions of IAS within 3 days (=one cycle) – “short term IA”

During the prolonged IAS program, one cycle was performed every 3 weeks.
Table 2. Effects of short-term IAS on renal disease and activity\textsuperscript{a,b}

<table>
<thead>
<tr>
<th></th>
<th>Start of IAS</th>
<th>3 Months IAS</th>
<th>12 Months IAS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients (n)</strong></td>
<td>11</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>IAS frequency (sessions/week)</strong></td>
<td></td>
<td>2.1 ± 0.7</td>
<td>0.7 ± 0.2</td>
<td></td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>9.2 ± 3.7</td>
<td>5.1 ± 3.1</td>
<td>2.3 ± 2.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>R20/R50 (%)</td>
<td>64/55</td>
<td>100/82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>24.7 ± 5.5</td>
<td>31.2 ± 4.4</td>
<td>37.5 ± 4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (mg/100 mL)</td>
<td>1.8 ± 0.8</td>
<td>1.4 ± 0.6</td>
<td>1.2 ± 0.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>58.9 ± 30.4</td>
<td>68.2 ± 27.9</td>
<td>74.5 ± 21.0</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>SLE activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLEDAI</td>
<td>19 ± 8</td>
<td>6 ± 6</td>
<td>4 ± 2</td>
<td>0.0004</td>
</tr>
<tr>
<td>R20/R50 (%)</td>
<td></td>
<td>100/73</td>
<td>100/100</td>
<td></td>
</tr>
<tr>
<td>SIS</td>
<td>14 ± 5</td>
<td>6 ± 2</td>
<td>4 ± 2</td>
<td>0.0002</td>
</tr>
<tr>
<td>ECLAM</td>
<td>8 ± 2</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-dsDNA (IU/mL)</td>
<td>168 ± 205</td>
<td>119 ± 185</td>
<td>45 ± 34</td>
<td>0.001</td>
</tr>
<tr>
<td>R20/R50 (%)</td>
<td></td>
<td>73/55</td>
<td>82/45</td>
<td></td>
</tr>
<tr>
<td>C3c (g/L)</td>
<td>52.1 ± 11.3</td>
<td>82.2 ± 17.9</td>
<td>92.6 ± 23.0</td>
<td>0.002</td>
</tr>
<tr>
<td>C4 (g/L)</td>
<td>11.0 ± 5.3</td>
<td>19.1 ± 5.1</td>
<td>18.9 ± 6.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\textsuperscript{a}SIS, SLE Index Score; ECLA, European Consensus Lupus Activity Measure.  

\textsuperscript{b}R20 = response 20 (i.e. reduction by 20\% compared to baseline), R50 = response 50 (i.e. reduction by 50\%), remission and partial remission as defined. For definition of activity scores (SLEDAI, SIS, ECLAM) see Subjects and methods section.
Fig. 2. Responses to prolonged IAS therapy. At the EoO, 10 (55%) patients under prolonged IAS showed a complete remission in all three outcome variables. Two patients in partial remission with respect to the primary outcome proteinuria were discontinued at their own request after showing a sustained response (Pat #9 and 10; proteinuria 0.59 and 0.68 g/day, respectively). In these patients, activity and dsDNA levels met the remission criteria. One additional patient showed a major response without completely reaching remission criteria at the EoO, although proteinuria was reduced by >70% (R70) compared to start of prolonged IAS (#5). One patient did not respond and was discontinued after a major renal flare (#7).
Immunoadsorption in Goodpasture’s syndrome

Laczika et al. 2000
Case report
Female patient, 28 years old

Dry eyes and mouth
Intermittent arthralgias
Joint symptoms with significant worsening before IA
Prednisolone 20 mg a day for 4 weeks
Methotrexate 25 mg a week without clinical benefit

Immunoadsorption:
  3 treatments on week 1
  2 treatments on week 5
Clinical outcome

After 1st week remarkable clinical improvement

- Lessening of arthralgias and articular swelling
- Increased joint mobility

SCORE for tender/swollen joints dropped from 29 to 0 at the end of study

C3 and C4 fell to 67% and 78% of baseline

Circulating immune complexes fell to 29%

Rheumatoid factor fell to 55% of baseline
Pat. 1: 43 years old, male, glomerulonephritis with 50% sclerosis

Pat. 2: 60 years old, female, necrotizing and sclerosing GN in >80% of glomeruli

Pat. 3: 58 year old, female, creatinine 453 µmol/L
FIG. 3. Displayed is the efficiency of anti-Proteinase 3 elimination by single immunoabsorptions for Patient B (A). The average reduction was approximately 80%, measured in serum before and directly after immunoabsorption (B).

FIG. 4. Complete and rapid elimination of anti-GBM and c-ANCA for >9 months by 11 immunoabsorptions and additional cyclophosphamide/methylprednisolone therapy is shown for Patient C. No recurrence of lung symptoms was seen. The patient stayed on dialysis.
Conclusion

- IA is more selective in eliminating pathological agents than TPE
- TPE has to use exchange fluids with all their potential side effects
- The schedules using IA are less time consuming than TPE schedules
- IA is chronic treatment, TPE is a acute treatment