Column therapy

Dr. Volker Witt
St. Anna Kinderspital
Vienna, Austria
About the LIPOSORBER System

The LIPOSORBER LDL-Adsorption Column

Selectively binds ApoB-containing lipoproteins (LDL, Lp(a) and VLDL). There is minimal effect on HDL or other plasma proteins.

- Dextran sulfate - cellulose bead
- LDL
- Lp(a)
- VLDL (Triglycerides)
- HDL
Evidence Based Therapeutic Apheresis

• Harmful Substance

• Meaningful Depletion

• Clinical Benefit
GENERAL PRINCIPLES
Therapeutic Plasmapheresis

Patient

separation

cells

Patient Plasma

Plasma substituted
TPE, how many times we should exchange the plasma volume?

\[ y^o = \text{absolute initial concentration} \]
\[ y^{abs} = \text{absolute final concentration} \]

\[ y^\% = \text{relative final concentration} \% \]
\[ e = \text{base of natural logarithms} \]
\[ x = \text{number of times the patient’s total plasma volume is exchanged} \]

\[ y^\% = e^{(-x)} \]

\[ y^{abs} = y^o \times (100 - y^\%) \]

---

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

Recovery of IgG => 45% in 48 hours
Replacement fluid

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

- n=190
  - Octaplas™

- n=74
  - HA 5 – 8%

- n=17
  - HA 5 – 8%
Recommendation

- 1 to 2 times the Plasma volume

- Start with 2 to 3 procedures and then think about the interval if not given by treatment schedule
Therapeutic Plasmapheresis

Patient

primary separation

Plasma plus Pathogen

Second separation

Plasma minus Pathogen

cells
Comparison of TPE and IA

1 liter human plasma protein (60 – 80g)

IgG (8 – 17 g)

IgG (8 – 17 g)

Pathogen < 1g
TECHNICAL ASPECTS IN IA
Immunoadsorption with regenerative columns
Immunoadsorption

Mast cell

Basophil

Allergen

IgE

FcεRI
Adsorptionssäulen

Zentrifuge

venöser Zugang
Ig removal – immunoabsorption

- 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.
Prediction of number of cycles needed => translation of PV in cycles of the system

Ig conc after %

11.4 % rest with 9 cycles
Prediction of processed Plasma Volume needed

Ig conc after %

0.0  2000  4000  6000  8000  10000

Processed Plasma volume [ml]

11.5 % rest with 1350 ml treated => 1.6 x PV
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

Immunadsorption
- 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:

- **START**
- **MAINTAINANCE**
- **TAPERING**
Target indications for TPE and IA

- Rheo Fibrinogen, CRP
  - Diabetic Foot Syndrome
  - Pulmonary Hypertension
  - Venous leg ulcer
- Ig antibodies
  - Atopic dermatitis
  - 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
- Plasma Exchange
  - IgE
    - Atopic dermatitis
    - Allergic asthma
    - Severe chronic urticaria
- LDL Lp(a)
  - Hypercholesterolemia
  - Pure Lp(a)
- LDL
  - Hypercholesterolemia
- Fibrinogen
- CRP
- Lp(a)
- LDL
  - Hypercholesterolemia
  - Pure Lp(a)
- Ig antibodies
  - Atopic dermatitis
  - Pulmonary Hypertension
  - Neurology
  - Solid Organ Transplantation
  - Hemophilia
  - Pemphigus
- Thrombangitis (Buerger's disease)
- Goodpasture's syndrome
- Kidney
- Heart
- Lung
- Liver
- Intestine
- ITP/TTP
- Sjögren's syndrome
- Systemic Sclerosis
- HUS
- Wegener's granulomatosis
- Goodpasture's syndrome
- Hypercholesterolemia
- Pure Lp(a)
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
Atopic dermatitis and ECP

• 11 studies performed
• 101 patients treated (57 male/39 female)
• 18 – 77 years old
• Response in 67 of 101 available

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>13%</td>
<td>39</td>
<td>22%</td>
<td>25%</td>
</tr>
</tbody>
</table>

75% any response
Apheresis

Weeks

1 2 3 4 5 6 7 8

Standard access: peripheral veins

Kasperkiewicz et al. JACI 2010, in press
IgE removal in atopic dermatitis

Source: University of Luebeck, Germany
Clinical outcome: SCORAD

![Graph showing SCORAD scores over time with mean values at before, week 5, and week 13.]

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
TheraSorb - IgE Adsorber

IgE concentration [IU/ml] vs. Treated plasma volume [%]

Graph showing the decrease in IgE concentration over treated plasma volume with TheraSorb IgE Adsorber and IgE-Adorber.
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></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[^1]

<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>1.4</td>
</tr>
</tbody>
</table>

Specific Removal of Anti A and Anti B antibodies  
= No unspecific adsorbtion 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
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.
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 short comings of one single form of therapy alone. J. Clin. Apheresis 28:56–63, 2013. © 2013 Wiley Periodicals, Inc.

Key words: antibody; apheresis; outcome; desensitization

IA alone?

• Not really
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.

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...
Targeting anti-beta-1-adrenergic receptor antibodies for dilated cardiomyopathy

Priyesh A. Patel and Adrian F. Hernandez

Duke Clinical Research Institute, Durham, NC, USA; and Duke University Medical Center, Durham, NC, USA

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Anti-beta-1-adrenergic receptor antibodies (anti-beta-1-AR Abs) have long been implicated in the pathogenesis of dilated cardiomyopathy (DCM). It is believed that these autoantibodies bind to and constitutively stimulate the beta-1AR to promote pathological cardiac remodelling and beta-1AR desensitization and downregulation. The prevalence of anti-beta-1-AR 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-beta-1-AR 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-beta-1-AR Abs, providing a hopeful avenue for future drug development to treat DCM. Herein, we briefly review the clinical literature of therapy directed against anti-beta-1-AR 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) [27]</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>Dorf et al. (1997) [30, 79]</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) [14, 30]</td>
<td>Non-selective IA</td>
<td>Prospective case-control (n = 34)</td>
<td>1 year</td>
<td>Improved EF; decreased markers of oxidative stress</td>
</tr>
<tr>
<td>Felix et al. (2000) [31]</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) [32]</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>Stautz et al. (2002) [25]</td>
<td>Non-selective IA vs. IA with low affinity for IgG3 (anti-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) [36]</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-AR Abs status</td>
</tr>
<tr>
<td>Knebel et al. (2004) [33]</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 hospitalization; improved NYHA class</td>
</tr>
<tr>
<td>Yoshihawa et al. (2009) [34]</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) [35]</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-AR Abs present</td>
</tr>
</tbody>
</table>

Ab, antibody; β,AR, 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) [36]</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) [37]</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) [38]</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) [39]</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-AR Abs and all other cardiodepressin Abs</td>
</tr>
<tr>
<td>Staudt et al. (2010) [40]</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) [9]</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-AR Abs were present at baseline</td>
</tr>
<tr>
<td>Wallukat et al. (2002) [11]</td>
<td>IA with peptide mimicking anti-beta-AR Ab epitope</td>
<td>Case series (n = 8)</td>
<td>1 year</td>
<td>Improved LVEF</td>
</tr>
<tr>
<td>Schimke et al. (2005) [41]</td>
<td>IA with peptide mimicking anti-beta-AR 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; β,AR, 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)

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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 immunoadsorption may decrease disease severity. TAO has been associated positively and negatively with various MHC class 1 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

Innate and adaptive immune response

Highly cellular intraluminal thrombus

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

Intraluminal thrombus with polymorphonuclear leukocytes, mononuclear cells, multinucleated giant cells

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

Endothelium

Adventitia

Intima

Media
... 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.
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.
... 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.
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\(^{a,b}\)

<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>Number of patients ((n))</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>IAS frequency (sessions/week)</td>
<td>2.1 ± 0.7</td>
<td>0.7 ± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal function</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>SLE activity</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>100/73</td>
<td>100/100</td>
<td></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>73/55</td>
<td>82/45</td>
<td></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>

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

\(^{b}\)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).
Rheopheresis

FIG. 1. Schematic drawing of the rheopheresis treatment, a specific application of double filtration plasmapheresis using the rheofilter as a plasma filter, in combination with appropriate pump technology (Octo Nova).
RheoNet Registry Analysis of Rheopheresis for Microcirculatory Disorders With a Focus on Age-Related Macular Degeneration

Reinhard Klingel,1,2 Cordula Fassbender,1 Andreas Heibges,1 Frank Koch,3 Joachim Nasemann,4 Katrin Engelmann,5 Thomas Carl,4 Michael Meinke,1 and Bernard Erdtracht6

1Apheresis Research Institute and 6Rheopheresis Center Cologne, Cologne, 2First Department of Internal Medicine, University of Mainz, Mainz, 3Department of Ophthalmology, University of Frankfurt, Frankfurt am Main, 4Clinic for Ophthalmology and Vitreoretinal Surgery, Munich, and 5Department of Ophthalmology, Chemnitz General Hospital, Chemnitz, Germany
Number and proportion of adverse events, vascular access problems, technical problems, and treatments without such events in 7722 rheopheresis treatments performed until December 2008 on 1110 patients (833 of whom had age-related macular degeneration)

<table>
<thead>
<tr>
<th>Treatments with reported events (all indications)</th>
<th>Class I</th>
<th>%</th>
<th>Class II</th>
<th>%</th>
<th>Class III</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (AE)</td>
<td>438</td>
<td>5.67</td>
<td>170</td>
<td>2.19</td>
<td>36</td>
<td>0.48</td>
</tr>
<tr>
<td>Technical problems (TP)</td>
<td>163</td>
<td>2.11</td>
<td>116</td>
<td>1.50</td>
<td>29</td>
<td>0.38</td>
</tr>
<tr>
<td>Vascular access problems (VAP)</td>
<td>425</td>
<td>5.50</td>
<td>155</td>
<td>2.01</td>
<td>60</td>
<td>0.78</td>
</tr>
<tr>
<td>Treatments without events (AE, TP, VAP)</td>
<td>6696</td>
<td>86.71</td>
<td>7281</td>
<td>94.28</td>
<td>7597</td>
<td>98.38</td>
</tr>
</tbody>
</table>

Class I: total reported events/problems; class II: reported events/problems requiring intervention or a temporary break in treatment; class III: reported events/problems requiring discontinuation of treatment. Class II is a subset of class I, and class III is a subset of class I and II.
FIG. 5. Visual acuity before rheopheresis treatment in relation to it after treatment—the proportion of eyes with improved, stable, and deteriorated visual acuity compared to baseline are shown. Improvement or deterioration in visual acuity was defined by a minimum change of one visual acuity level (≥0.1 log(Mar)), in general corresponding to one line on a visual acuity chart. N = 428 eyes with dry AMD of 279 patients. Patients received an average of 8.1 ± 1.6 treatments within 15 ± 14 weeks, with an average 6.75 ± 5.25 months’ interval between the baseline and follow-up ophthalmological examinations.
Proportion of cases with gain and loss in visual acuity at 6.75 ± 5.25 months post-baseline in the rheopheresis treatment group versus the control population (without treatment) at 6.00 ± 3.00 months post-baseline (P < 0.01). Gain or loss in visual acuity was defined by a minimum change of one visual acuity level (± 0.1 log(Mar)), in general corresponding to one line of a visual acuity chart. The comparison of proportions was performed with the X2-test for cross tabulated data.
CRP-Adsorber - PentraSorb® CRP

**Indications:**
- Acute myocardial infarction
- Stroke
- Global cerebral ischemia after resuscitation
- Diseases of the rheumatic form circle
Ten pigs received balloon catheter-induced myocardial infarction. CRP was depleted from five animals utilizing a new specific CRP-adsorber, five animals served as controls.

CRP-apheresis resulted in a mean reduction of the CRP levels up to 48.3%. The area of infarction was significantly reduced by 30 6 6% (P 5 0.003) within 14 days in the treatment group, whereas it increased by 19 6 11% (P 5 0.260) in the controls. Fourteen days after infarction, the infarcted area revealed compact, transmural scars in the controls, whereas animals receiving CRP-apheresis showed spotted scar morphology. In the interventional group, a significantly higher left ventricular ejection fraction (LVEF) was observed after 14 days as compared to the controls (57.6 6 2.4% vs. 46.4 6 2.7%; P 5 0.007).

In a pig model for AMI, we observed that selective CRP-apheresis significantly reduces CRP levels and the volume of the infarction zone after AMI. Additionally, it changes the morphology of the scars and preserves cardiac output (LVEF).
Fig. 1. CRP kinetics after CRP-apheresis in comparison to the controls. The timing of vascular access (Shaldon-catheter insertion) placement is given by the arrow (removal on day 9), duration of infarction (balloon catheter intervention) is highlighted by red bar. The first apheresis (apheresis I) was conducted 18–20 h after AMI followed by a second treatment 24 h later (apheresis II). Apheresis treatments are highlighted by green bars. CRP concentrations were measured directly before and after the apheresis. Hours are stated in relation to the time of infarct induction. Standard deviation is shown in one direction only. * = significant. Please note that CRP synthesis was more pronounced on first apheresis than on second apheresis. An increase of CRP in the interventional group in postapheresis days is most likely due to the experimental design (see discussion). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Fig. 3. Slices of the left ventricle 14 days after acute myocardial infarction. Slices were generated after an Evans Blue staining of the heart (staining artefacts are visible in the connective tissue). Circles localize characteristic transmural scar of a control animal (left) versus spotted scar morphology after CRP-apheresis (right).
Structure and composition of endotoxin and ET-binding proteins

Schematic drawing of loop structure of endotoxin-binding domain of r Limulus anti-lipopolysaccharide factor (J Biol Chem 271 (1996) 28120) rich in lysine (K, basic AS), but also some tryptophan (W, aromatic, hydrophobic) and histidine (H, basic) amino acids.

Structure of Lipopolysaccharide

O-antigen repeat 40 units
Core polysaccharide
Disaccharide diphosphate
Fatty acids

Structure of Lipid A domain of endotoxin lipopolysaccharide with hydrophobic fatty acid domain and negatively charged.
Functionalized nanoparticles for endotoxin binding in aqueous solutions


Biomaterials 20 (1999) 1277–1283

Development of nanoparticles with high aspect ratio for adsorptive binding of ET in MDS system \( \rightarrow \) biomimetic approach to use Coulomb and hydrophobic interaction either based on amino acids or synthetic molecules

Conversion of epoxide group and particle charge of nanoparticle

<table>
<thead>
<tr>
<th>Type of ligand</th>
<th>Conversion of epoxide group (mol%)</th>
<th>Particle charge density (µC/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrolyzed OH</td>
<td>100</td>
<td>-1.03</td>
</tr>
<tr>
<td>Ethylene diamine EDA</td>
<td>30</td>
<td>+5.5</td>
</tr>
<tr>
<td>Hexamethylene diamine HDA</td>
<td>50</td>
<td>+1.34</td>
</tr>
<tr>
<td>Dodecyl diamine DODA</td>
<td>30</td>
<td>+3.3</td>
</tr>
<tr>
<td>Histamine HisA</td>
<td>30</td>
<td>+2.0</td>
</tr>
<tr>
<td>Tryptamine TrpA</td>
<td>50</td>
<td>+2.05</td>
</tr>
<tr>
<td>Lysine LyS</td>
<td>50</td>
<td>-0.4</td>
</tr>
<tr>
<td>Tryptophan Trp</td>
<td>10</td>
<td>-2.04</td>
</tr>
<tr>
<td>Histidine His</td>
<td>10</td>
<td>+2.2</td>
</tr>
<tr>
<td>Tetracaine TC</td>
<td>10</td>
<td>+0.94</td>
</tr>
<tr>
<td>Polymyxin B PMXB</td>
<td>n.a.</td>
<td>+3.9</td>
</tr>
<tr>
<td>Polyethylene imine PEI</td>
<td>n.a.</td>
<td>+1.72</td>
</tr>
</tbody>
</table>

n.a.: Not assessable.

St = styrene; GMA = glycidyl methacrylate; NH₃R = ligand; (i): T = 60°C, t = 16h, K₂S₂O₈; C₁₂H₂₅Na₂O₄S; (ii): T = 60°C, t = 8h; (iii): T = 40°C, t = 48h, pH = 9

DOI: 10.1159/000098434
Results of endotoxin binding on nano nanoparticles with biomimetic ligands

Binding of single amino acids like lysine ⇀ bind ET only in water, Removal of negatively charged carboxylic groups ⇀ increases of ET adsorption on tryptophane and histidine.
Addition of salt ⇀ reduces Coulomb interaction of amino acids.
Synthetic, strongly cationic ligand poly (ethylen imine. PEI) most effective ⇀ indicating important role of Coulomb interaction for ET binding
Particles not used in MDS ⇀ too small particles could pass plasma filtration membrane ⇀ Safety concerns for patients
Extracorporeal cell therapy of septic shock patients with donor granulocytes: a pilot study

Jens Altrichter¹, Martin Sauer², Katharina Kaftan¹, Thomas Birken², Doris Gloger³, Martin Gloger⁴, Jörg Henschel⁴, Heiko Hickstein¹, Ernst Klar⁵, Sebastian Koball¹, Annette Pertschy⁵, Gabriele Nöldge-Schomburg², Dierk A Vagts² and Steffen R Mitzner¹*
Methods

• The trial was conducted as a prospective uncontrolled clinical phase I/II study with 28-day follow-up at three university hospital intensive care units.

• Ten consecutive patients (five men, five women, mean age 60.3 ± 13.9 standard deviation (SD) years) with septic shock with mean ICU entrance scores of Acute Physiology and Chronic Health Evaluation (APACHE) II of 29.9 ± 7.2 and of Simplified Acute Physiology Score (SAPS) II of 66.2 ± 19.5 were treated twice within 72 hours for a mean of 342 ± 64 minutes/treatment with an extracorporeal bioreactor containing 1.41 ± 0.43 × 10E10 granulocytes from healthy donors.

• On average, 9.8 ± 2.3 liters separated plasma were treated by the therapeutic donor cells.
Schematic drawing of the extracorporeal treatment. Plasma is separated from blood, transferred to the cell-compartment, and then returned to the patient.

Alrichter et al. Critical Care 2011
Results

• The extracorporeal treatments were well tolerated.
• During the treatments, the bacterial endotoxin concentration showed significant reduction.
• ... noradrenaline dosage could be significantly reduced ...
• ... C-reactive protein, procalcitonin, and human leukocyte antigen DR (HLA-DR) showed significant improvement.
• Four patients died in the hospital on days 6, 9, 18 and 40.
• Six patients could be discharged.
Tissue banking and artificial organs

Tissue engineering for repair of injured tissues by combination of degradable materials with cells. Bioartificial organs for temporary replacement in acute organ failure of liver and kidney as combination of machine and cell based blood purification.
Biomimetics in artificial organ technology and tissue engineering

In 1969 the term biomimetics was used by Otto Schmitt to title one of his papers → "a science concerned with the application of data about the functioning of biological systems to the solution of engineering problems".

Microfluidic model of the platelet-generating organ: beyond bone marrow biomimetics – Scientific Reports 2016

David W. Green et al. J. R. Soc. Interface 2014;11:20140537
Layer by Layer Technique – Adsorption of glycosaminoglycans to obtain nanostructured surfaces

Sequential & repeated adsorption of polyions onto a charged substrate from dilute solutions by electrostatic attraction, ion pairing, hydrogen bonding and covalent linkage

Comparison of surface topography of multilayers prepared from heparin (−) and chitosan (+) either at pH 5 (left image) or pH 9 (right image) visualised with AFM

Heparin & other sulfated GAGs and polysaccharides → polyanions

Chitosan and proteins like collagen I → polycations

Niepel et al. 2014
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 an acute treatment
• Columns are available for an increasing amount of pathogens
• Columns could host „artefical organs“
• Nevertheless it must show in prospective trials its position in the treatment schedules in different diseases.