Double Column Immunoadsorption

–

An Effective Therapeutic Option In Immune Mediated Diseases

Bernd Hohenstein, MD
Extracorporeal Treatment and Apheresis Center
& Division of Nephrology
Department of Internal Medicine III,
University Hospital Carl Gustav Carus
Dresden, Germany
Financial Disclosures

Speaker honoraries and honoraries for advisory boards as well as congress travel support and research funding were provided by (alphabetical order):

Alexion, Amgen, Astellas, B. Braun Avitum, Bristol-Myers Squibb, ChemoCentryx, Fresenius Medical Care, Kaneka Pharma Europe, MSD Sharp & Dohme, Miltenyi Biotec, Novartis, Omeros, Roche, RIGEL Pharmaceuticals, Sanofi/Regeneron
Clinical case

♀, 33 years, M.D.

Acute motosensory loss of the lower extremities
-> standing with help, no walking possible
CT and MRI scans: inconclusive, possibly acute MS

Patient refused to receive high dose steroid therapy
(1-2g for 5 days)

→ Decision to start immunoadsorption therapy
Apheresis Center in Dresden, Germany

12 fully equipped treatment seats, 5 days/week, 2 shifts

2014:

>4000 lipoprotein apheresis treatments

>400 immunoadsorptions
Dresden University Apheresis Center
Immunoadsorption - Division of Nephrology

All nephrological patients and preferentially transplant patients
- ABOi
- Desensitization
- Acute humoral rejections

In 2014: 50 IA sessions
Mechanisms of action for PE or IA

- Immediate intravascular reduction of (auto-)antibody concentration
- Pulsed induction of antibody redistribution
- Subsequent immunomodulatory changes
Available IA columns

- **Ig-columns** coated with sheep-Ig directed against human Ig
  (Therasorb®-Ig, Miltenyi Biotec, Bergisch-Gladbach, Germany)

- **protein A columns** with staphylococcal Protein A
  (Immunosorba®, Fresenius Medical Care, Bad Homburg, Germany)

- **GAM-columns** made with the synthetic peptide Gam 146
  (Globaffin®, Fresenius Medical Care, Bad Homburg, Germany)

- **dextran sulfate bound columns**
  (Selesorb®, Kaneka Medical Products, Osaka, Japan)

- **Tryptophane or Phenyl-alanine coated columns** which represent an option for patients with protein allergies
  (Immusorba®, Asahi Kasei Medical, Tokyo, Japan)

- **IgE-columns**
  (Therasorb®-IgE, Miltenyi Biotec, Bergisch-Gladbach, Germany)

- **Ig-κ and λ-light-chain columns**
  (Therasorb®-Ig omni, Miltenyi Biotec, Bergisch-Gladbach, Germany)
Does IA cause off-target effects? IgG and C3 levels with TR-IA

A

Baseline

IA

Follow-up

sign.

sign.

sign.

B

Baseline

IA

Follow-up

sign.

sign.

sign.
Beneficial side effects of IA


Effect of immunoadsorption on Sc5b-9 in a single patient

1 therapy session

Effect of immunoadsorption on Sc5b-9 in a single patient

Beneficial side effects of IA

When should PE or IA be considered (in general)

- Clear antibody mediated and preferentially acute disease
- Antibody mediated disease, not sufficiently treated by pharmacological approaches
- Patients who can’t tolerate pharmacotherapy
- Patients with high risk under immunosuppression
  - tuberculosis
  - pregnancy
  - tumors
Why Immunoadsorption instead of plasma exchange?

- Easily applicable (possible without central venous access)
- Superior efficacy, spec. with respect to antibody depletion
- Higher selectivity (with ongoing improvements)
- No plasma or albumin substitution necessary
- No risk for transmission of blood borne infectious disease
- Reduced allergic reactions
- Very good safety, especially when compared to PE with albumin substitution
First description:

IA in Myasthenia gravis

Pilot Study (proof of concept, IA, adjusted to PE efficacy)

- 20 patients, 18-80 yrs old
- Class 4 or worse according to the classification of Oosterhuis
- Long-term treatment of myasthenia gravis with
  - acetylcholinesterase inhibitors
  - steroids,
  - and others (IvIG, Thymectomy)

Inclusion criteria

- established impairment or imminent respiratory failure
- severe dysphagia with risk of aspiration
- walking distance below five meters

Equal response with PE vs IA in Myasthenia gravis

### TABLE III. Adverse Events with PE or IA During the Treatment Period

<table>
<thead>
<tr>
<th>Event</th>
<th>PE (32 treatments)</th>
<th>IA (30 treatments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[N] patients with SAE/AE</td>
<td>7/10 (70%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>total (SAE/AE)</td>
<td>23 (7/16)</td>
<td>11 (1/10)</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Haematoma</td>
<td>3 (2 SAE)</td>
<td>0</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia, hypotension</td>
<td>2 (2 SAE)</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (SAE)</td>
<td>3 (1 SAE)</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>1 (SAE)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2 (1 SAE)</td>
<td>1</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cystitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypokaliaemia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Malaise</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Photopsia</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
# Trials of PE and/or IA for neurologic disorders

<table>
<thead>
<tr>
<th>Trial/investigation</th>
<th>Design</th>
<th>Sample size</th>
<th>Results, remarks</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma exchange (PE)</strong>&lt;br&gt;Immunosuppression + PE (progr. or relap./remit.)</td>
<td>Random., double-blind sham-PE controlled, ACTH/cyclophosph. + apheresis</td>
<td>$N = 76$ (out of 116)</td>
<td>PE patients with relapsing/remitting MS had significantly enhanced improvement at 4 weeks, no results for long-term benefit</td>
<td>[12]</td>
</tr>
<tr>
<td>PE escalation in acute CNS-IDD (no pre-existing progressive MS)</td>
<td>Random., cross-over, double-masked sham-PE controlled, 7 apheresis after failure of iv steroids</td>
<td>$N = 22$ (12 MS)</td>
<td>42.1% vs 5.9% showed improvement with PE vs sham in acute neurological deficits of inflammatory demyelinating disease after failure of iv steroids</td>
<td>[13]</td>
</tr>
<tr>
<td>Relation of humoral pathologic changes and response to PE</td>
<td>Retrospective, case series</td>
<td>$N = 19$</td>
<td>MS patients with pattern II pathology showed 100% response</td>
<td>[8]</td>
</tr>
<tr>
<td><strong>PE for steroid unresponsive multiple sclerosis relapses</strong>&lt;br&gt;Relap.—remit. incl. subgroup optic neuritis</td>
<td>Retrospective cohort trial</td>
<td>$N = 35$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Retrospective case series (2005–08)</td>
<td>$N = 20$ (73 MS, 26 NMO)</td>
<td>with optic neuritis, 87.5% with other symptoms 59% moderate to marked functional neurological improvement</td>
<td>[14]</td>
</tr>
<tr>
<td><strong>Response to PE in acute steroid-refractory CNS-IDD</strong>&lt;br&gt;Immunoadsorption (IA)&lt;br&gt;Tryptophan-IA prolonged severe relapse</td>
<td>Case series</td>
<td>$N = 3$</td>
<td>100% response after 5–6 IA within 7–10 days</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td>Case</td>
<td>$N = 1$ (out of 35 PE)</td>
<td>Response of 3rd relapse with optic neuritis within 1 yr</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis of case series</td>
<td>$N = 14$</td>
<td>86% response; 6 pts. with optic neuritis</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
<td>$N = 10$ (5 PE, 5 IA)</td>
<td>Diagnosis: MS 5, ADEM 3, NMO 2; 90% response; 4 pts. with optic neuritis</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td>Prospective uncontrolled trial</td>
<td>$N = 10$</td>
<td>Marked-moderate response in 66%</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td>Prospective uncontrolled trial</td>
<td>$N = 11$</td>
<td>73% response (8/11) with optic neuritis</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis of case series</td>
<td>$N = 24$</td>
<td>67% (12/18) response; 100% (6/6) response with optic neuritis</td>
<td>[21]</td>
</tr>
</tbody>
</table>

**Most trials are retrospective!**
Studies in MS using Immunoadsorption

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>Study type</th>
<th>MS-type</th>
<th>Corticosteroid-refractory</th>
<th>IA-treatments/patient</th>
<th>Treated plasma volume</th>
<th>Ligand</th>
<th>Treatment period</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[21]</td>
<td>1989</td>
<td>16</td>
<td>Retrospective</td>
<td>Chronic progressive RRMS</td>
<td>No</td>
<td>&gt;10</td>
<td>3000 ml</td>
<td>Tryptophan</td>
<td>6 months</td>
<td>EDSS-improvement</td>
</tr>
<tr>
<td>[22]</td>
<td>2000</td>
<td>3</td>
<td>Retrospective</td>
<td>RRMS</td>
<td>Yes</td>
<td>5–6</td>
<td>n.a.</td>
<td>n.a.</td>
<td>7–10 days</td>
<td>Clinical response in all three patients</td>
</tr>
<tr>
<td>[23]</td>
<td>2005</td>
<td>12</td>
<td>Prospective</td>
<td>RRMS SPMS</td>
<td>No</td>
<td>14</td>
<td>1.5-fold plasma volume</td>
<td>Sepharose-conjugated Sheep antibodies to human Ig</td>
<td>90 days</td>
<td>No significant improvement of neurological capacities</td>
</tr>
<tr>
<td>[24]</td>
<td>2011</td>
<td>14</td>
<td>Retrospective</td>
<td>RRMS</td>
<td>Yes</td>
<td>5–6</td>
<td>n.a.</td>
<td>Tryptophan</td>
<td>13 ± 8 days</td>
<td>Significant improvement in 12 of 14 patients</td>
</tr>
<tr>
<td>[25]</td>
<td>2012</td>
<td>10</td>
<td>Retrospective</td>
<td>8 RRMS 2 clinical isolated syndromes</td>
<td>Yes</td>
<td>5–7</td>
<td>2500</td>
<td>Tryptophan</td>
<td>n.a.</td>
<td>Significant improvement in 8 of 10 cases</td>
</tr>
<tr>
<td>[20]</td>
<td>2012</td>
<td>11</td>
<td>Prospective</td>
<td>RRMS with acute optic neuritis</td>
<td>Yes</td>
<td>5</td>
<td>2500</td>
<td>Tryptophan</td>
<td>9–11 days</td>
<td>Significant improvement in 8 of 11 cases of optic neuritis</td>
</tr>
</tbody>
</table>

Today: 14:00 Gran Cancun 5: Immunoadsorption in Neurological Disease
Variable recommendations in different countries - USA

Disease Modifying Therapies in Multiple Sclerosis
February 2002 Current guideline.
Reaffirmed October 17, 2003 and July 19, 2008.

Plasma exchange
1. On the basis of consistent Class I, II, and III studies, plasma exchange is of little or no value in the treatment of progressive MS (Type A recommendation).
2. On the basis of a single small Class I study, it is considered possible that plasma exchange may be helpful in the treatment of severe acute episodes of demyelination in previously nondisabled individuals (Type C recommendation).
Variable recommendations in different countries - Germany

<table>
<thead>
<tr>
<th>Indikation</th>
<th>CIS¹</th>
<th>RRMS¹</th>
<th>SPMS¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eskalationstherapie</td>
<td>Glatirameracetat, Interferon-β 1a i.m., Interferon-β 1a s.c., Interferon-β 1b s.c.</td>
<td>Glatirameracetat, Natalizumab⁴, (− Cyclophosphamid)⁵</td>
<td>Mitoxantron, (− Cyclophosphamid)⁵</td>
</tr>
<tr>
<td>Basistherapie</td>
<td>2. Wahl – Fingolimod⁴ – Mitoxantron (− Cyclophosphamid)⁵</td>
<td>1. Wahl – Interferon-β 1a s.c., Interferon-β 1b s.c., (− Azathioprin)² (− IVig)³</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Schubtherapie</th>
<th>2. Wahl</th>
<th>1st choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute</td>
<td>2nd choice</td>
<td>Methylprednisolonpuls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasmaseparation</td>
</tr>
</tbody>
</table>

The likelihood of improvement in non-steroid responsive patients receiving plasma exchange is up to 70%, if the acute progression is not lasting for more than 6 weeks. Indiviudall response after a longer time period has been reported.
Most studies have been performed with Tryptophane IA (TR-IA)

Tryptophane immobilized in polyvinyl alcohol gel

Binds Ig via hydrophobic interaction
- variable binding capacity for Ig
- binding of other proteins (such as coagulation factors)
- maximum plasma volume: 2.5 liters

Good binding of
- anti-DNS ab and immune complexes

Moderate binding of
- anti-phospholipid ab
- rheumatoid factors

Immusorba TR®
IA systems – are there differences?

IA in bullous pemphigus using TR-IA

<table>
<thead>
<tr>
<th>IgG reduction %</th>
<th>Total protein reduction %</th>
<th>Effective IgG reduction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>40</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>48</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>49</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>44</td>
<td>22</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Σ: Single use columns were less effective than re-usable columns, which generated a IgG reduction of up to 80%!
Why double-column systems instead of one-way systems?

Considerations:

- Superior efficacy
- Systems become more selective
- Processing of very large plasma volumes
- Re-Usable up to x10, x20 or even more often
- Can be used for months and years
- Cost effective for long term treatment
Immunoadsorption using the Art Universal – Adasorb System

Vascular access: dialysis fistula or catheter
Plasma volume: x 2 – 2.5
Anticoagulation: Heparin/Citrate
Re-Usability: 10-15 x
Immunoadsorption using COM.TEC-ADASORB
since 2012 in Dresden

- Immunoadsorption using Globaffin (Peptid GAM®)-columns and the Art Universal-Adasorb-System

- Starting 2014 use of Immunosorba®-Columns and plasma separation using the COM.TEC®-Zentrifuge

- Combination with „MONET“ for removal of IgM – Isoagglutininins
Immunoadsorption – extracorporeal circuit

==TheraSorb™ Therapeutic Apheresis==

**Very low extracorporeal volume**

- Anticoagulant
- Plasma separation

- Adsorption
- Regeneration
- Waste

- 50 ml
- 80 ml

Courtesy of Miltenyi Biotech
The Disc Separator separates blood cells and plasma by ultrafiltration and centrifugation.

Blood volume: 22 mL
Plasma volume: 15 mL

Courtesy of Miltenyi Biotech
Principle of Disc separation

The rotation of blood prevents red blood cells from clogging the ultrafiltration membrane

Courtesy of Miltenyi Biotech
Use of the disc system is excellent in small patients

The smallest patient was 7 months old with 6.3 kg body weight

Diagnosis: severe heart failure due to dilated cardiomyopathy

Total blood volume 480 mL

7 french central catheter

Blood flow 11 mL/min

Plasma flow 5 mL/min
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>
Ig levels during 5-days IA

Data from Study 'Atopic Dermatitis', Patient 1, series 1

0%
20%
40%
60%
80%
100%
120%

28.01.08 29.01.08 30.01.08 31.01.08 01.02.08 02.02.08
Date

Source: University of Luebeck, Prof. Zillikens
Double column IA: The Dresden experience

Treatment indications

- Generalized myasthenia gravis
- Multiple sclerosis with optical neuritis
- Myelitis transversa
- Myasthenia gravis
- Guillain-Barre-Syndrome
- Autoimmune cerebellitis, unknown origin
- Autoimmune encephalitis with GAD antibodies
- Cerebellar ataxia
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Progressive encephalomyelitis with rigidity and myoclonus (PERM) syndrome
- Paraneoplastic cerebellitis
- Pemphigus vulgaris
- Atopic dermatitis
- Lichen myxedematosus
- Hämatopoeitic stem cell transplantation
- Hämophilia
- ABOi kidney transplantation
- Kidney recipient desentization
- Acute humoral kidney transplant rejection

Neurology

Dermatology

Hematology

Nephrology /KTx

and unclear disorders
IA in neurological indications using Therasorb®-Ig columns

Parameter (mean)

- treated plasma volume (x PV): 2.2
- treated blood volume (l): 15.6
- treated plasma volume (l): 5.01
Double column systems provide highly effective, titrable Ig reduction

Hohenstein et al., Atheroscler Suppl. 2015 May;18:119-23
Our Case

Treatment approach with IA
- 10 treatment sessions, first week daily, then alternating
- Target 2x plasma volume
- Well tolerated, no problems with peripheral venous access

Outcome
- Steadily improving motoric and sensoric capabilities during treatment
- Successful application of 10 treatment sessions
- Finally full restitution
- Further neurologic evaluation and controls
Target indications for immunoadsorption therapy

**IgE adsorption**
- Atopic dermatitis
- Myasthenia gravis
- Guillain-Barré syndrome
- Lambert-Eaton syndrome
- Devic’s syndrome
- Multiple sclerosis
- Encephalitis
- CIDP

**Ig antibody adsorption**
- Lupus erythematosus
- Dilated Cardiomyopathy
- Neurology
- Pulmonary Hypertension
- Hemophilia
- Pemphigus

**K and λ adsorption**
- Hemolytic anemia
- ITP/TTP
- Sjögren’s syndrome
- Systemic Sclerosis
- HUS
- Wegener’s granulomatosis
- Goodpasture’s syndrome
- Thrombangitis (Buerger’s disease)
- Solid Organ Transplantation
- Kidney
- Heart
- Lung
- Liver
- Intestine

**Plasma Exchange**
- Plasma
- Exchange

**sFLT1 adsorption**
- Multiple sclerosis
- Encephalitis

Hohenstein 2015
Summary

- IA effectively removes Ig from large plasma volumes (except for TR-IA)
- IA can be easily applied and is safe
- IA should be considered in acute ab mediated disorders
  (especially as an adjuvant therapy to pharmacological targeting of ab production)
- IA should be considered in patients not eligible for immunosuppression
- Proof-of-concept data of good quality for few indications (myasthenia gravis, multiple sclerosis)
- Prospective, randomized studies are necessary for practically all indications
- We also need to improve our understanding of IA effects apart from ab removal
Thanks for your attention!