Immunoadsorption as an alternative approach for the treatment of autoimmune disease of the nervous system

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First description:
Hosokawa S, Oyamaguchi A, Yoshida O.
Successful immunoadsorption with membrane plasmapheresis for multiple sclerosis.

Antibody targets in neurological disorders

Corresponding antigens of anti-neuronal antibodies associated with encephalitis [32,33,35–37].

**Cell surface antigens**

VGKC-complex (voltage-gated potassium channel complex)

- LGII (leucine-rich glioma inactivated 1)
- CASPR2 (contactin-associated protein 2)

NMDAR (N-methyl-d-aspartate receptor)

AMPAR (α-amino-3-hydroxi-5-methyl-4-isoaxazol-propionic-acid receptor)

GABA_BR (γ-amino-butyric-acid type B receptor)

GlyR (glycine receptor)

**Intracellular antigens**

Onco-neural (in app. 90% para-neoplastic)

- Hu (neuronal nuclear antigen type 1, RNA binding)
- Ri (neuronal nuclear antigen type 2)
- Amphiphysin (surface of synaptic vesicles)
- Yo, CV2, Ma 1–3 (RNA biogenesis), Tr
- CRMP-5 (collapsin-response mediator protein-5)
- Purkinje-cell cytoplasmic antigen 1,2
- GAD (glutamic acid decarboxylase)
Target indications for immunoadsorption therapy

- Ig antibody adsorption
- Hemolytic anemia
- ITP/TTP
- Systemic Sclerosis
- HUS
- Wegener’s granulomatosis
- Goodpasture’s syndrome
- Thrombangitis (Buerger’s disease)
- Solid Organ Transplantation
- Plasma Exchange

- Neurology
  - Myasthenia gravis
  - Guillain-Barré syndrome
  - Lambert-Eaton syndrome
  - Devic’s syndrome
  - Multiple sclerosis
  - Encephalitis
  - CIPD
- Pulmonary Hypertension
- Pemphigus
- Hemophilia
- Hemophelia
- Solid Organ Transplantation
  - Kidney
  - Heart
  - Lung
  - Liver
  - Intestine
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

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. Individually response after a longer time period has been reported.
Mechanisms of action for PE or IA

- Immediate intravascular reduction of (auto-)antibody concentration
- Pulsed induction of antibody redistribution
- Subsequent immunomodulatory changes
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)
- Possible with regional citrate anticoagulation
- Superior efficacy (up to 2.5 - 3x plasma volume treated)
- No plasma or albumin substitution necessary
- No risk for blood borne infectious disease
- Reduced allergic reactions
- Very good safety, especially when compared to PE with albumin substitution
Available IA columns

- **Ig-columns** coated with sheep-Ig directed against human Ig
  (Ig-Therasorb®, 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)
Immunoabsorption – extracorporeal circuit

TheraSorb™ Therapeutic Apheresis

Very low extracorporeal volume

80 ml

Anticoagulant

Plasma separation

Regeneration

50 ml

Adsorption

Waste

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
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 liter

Good binding of
- anti-DNS ab and immune complexes

Moderate binding of
- anti-phospholipid ab
- rheumatoid factors
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>

∑: Single use columns were less effective than re-usable columns, which generated a IgG reduction of up to 80%!
### 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></td>
<td>Random., double-blind sham-PE, ACTH/</td>
<td>( N = 76 )</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>(progr. or relap/remit.)</td>
<td>cyclophosph. + apheresis</td>
<td>(out of 116)</td>
<td>(12 MS)</td>
<td>[13]</td>
</tr>
<tr>
<td>PE escalation in acute CNS-IDD (no pre-existing progressive MS)</td>
<td>Random., cross-over, double-masked sham-PE</td>
<td>( N = 22 )</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></td>
<td>controlled, 7 apheresis after failure of iv steroids</td>
<td></td>
<td>(12 MS)</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>PE for steroid unresponsive multiple sclerosis relapses</td>
<td>Retrospective cohort trial</td>
<td>( N = 35 )</td>
<td>71% of patients with functionally relevant improvement</td>
<td>[15]</td>
</tr>
<tr>
<td>Relap.—remit. incl. subgroup optic neuritis</td>
<td>Retrospective case series (2005—08)</td>
<td>( N = 20 )</td>
<td>Marked-moderate response in 76% with optic neuritis, 87.5% with other symptoms</td>
<td>[16]</td>
</tr>
<tr>
<td>Response to PE in acute steroid-refractory CNS-IDD</td>
<td>Retrospective cohort trial (1999—2007)</td>
<td>( N = 153 )</td>
<td>59% moderate to marked functional neurological improvement</td>
<td>[14]</td>
</tr>
<tr>
<td><strong>Immunoadsorption (IA)</strong></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>Tryptophan-IA prolonged severe relapse</td>
<td>Case</td>
<td>1 (out of 35 PE)</td>
<td>Response of 3rd relapse with optic neuritis within 1 yr</td>
<td>[15]</td>
</tr>
<tr>
<td>Tryptophan-IA for steroid-unresponsive MS relapse with optic neuritis</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>Tryptophan-IA for steroid-unresponsive MS</td>
<td>Case series</td>
<td>( N = 10 )</td>
<td>Diagnosis: MS 5, ADEM 3, NMO 2; 90% response; 4 pts. with optic neuritis</td>
<td>[18]</td>
</tr>
<tr>
<td>PE or tryptophan-IA for pediatric acute CNS-IDD</td>
<td>Prospective uncontrolled trial</td>
<td>( N = 10 )</td>
<td>Marked-moderate response in 66%</td>
<td>[22]</td>
</tr>
<tr>
<td>Tryptophan-IA for steroid-unresponsive MS relapse with optic neuritis</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>Tryptophan-IA for steroid-unresponsive MS relapse</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>
PE vs IA for 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

PE vs IA for Myasthenia gravis
Baseline data

### TABLE II. Baseline Characteristics of Enrolled Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PE (n = 10)</th>
<th>IA (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.7 ± 12.9</td>
<td>62.3 ± 11.8</td>
</tr>
<tr>
<td>Sex (no., %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (40%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (60%)</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>62.9 ± 11.9</td>
<td>68.9 ± 14.4</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>168.8 ± 6.8</td>
<td>168 ± 8.3</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>54.1 ± 21.6</td>
<td>49.9 ± 17.1</td>
</tr>
<tr>
<td>Duration of MG (years)</td>
<td>6.8 ± 8.9</td>
<td>11.9 ± 12.4</td>
</tr>
<tr>
<td>Baseline myasthenia score</td>
<td>21.3 ± 4.3</td>
<td>19 ± 2.2</td>
</tr>
<tr>
<td>Modified myasthenia score at baseline</td>
<td>2.6 ± 0.3</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Last myasthenic crisis (months)</td>
<td>22.9 ± 42.1</td>
<td>5.1 ± 6.3</td>
</tr>
<tr>
<td>Former therapies (no. of pts.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressives</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>PE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IA</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD.

Equal response with PE vs IA in Myasthenia gravis
Less side effects with IA vs PE

<table>
<thead>
<tr>
<th>TABLE III. Adverse Events with PE or IA During the Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>PE (32 treatments)</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>[N] patients with SAE/AE</td>
</tr>
<tr>
<td>total (SAE/AE)</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Haematoma</td>
</tr>
<tr>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Bradycardia, hypotension</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Hypersalivation</td>
</tr>
<tr>
<td>Dyspnœa</td>
</tr>
<tr>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Cystitis</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Hypokaliaemia</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
<tr>
<td>Psychosis</td>
</tr>
<tr>
<td>Photopsia</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Immunoadsorption is effective in Multiple Sclerosis

Immunoadsorption in 60 patients (21 m, 39 f) with steroid-refractory MS relapses: the main symptoms and the primary clinical responses.

<table>
<thead>
<tr>
<th>Main symptoms of MS</th>
<th>No. of patients</th>
<th>No. of primary clinical responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS optic neuritis</td>
<td>26</td>
<td>23 (88.5%)</td>
</tr>
<tr>
<td>MS spastic paresis</td>
<td>26</td>
<td>23 (88.5%)</td>
</tr>
<tr>
<td>MS sensory deficit</td>
<td>5</td>
<td>4 (80.0%)</td>
</tr>
<tr>
<td>MS brain stem symptoms</td>
<td>3</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>$\sum MS$</td>
<td>60</td>
<td>53 (88.3%)</td>
</tr>
</tbody>
</table>
Response to IA in refractory MS

Koziolek et al., Atherosclerosis Supplements 14 (2013) 167-173
IA use for neurological disorders
The Dresden experience

Indications:

• Generalized myasthenia gravis
• Multiple sclerosis with optical neuritis
• Myelitis transversa
• Autoimmune cerebellitis
• Autoimmune encephalitis with GAD antibodies
• Cerebellar ataxia
### IA in neurological indications - treatment overview

**Parameter (mean)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>treated plasma volume (x PV)</td>
<td>2.00</td>
</tr>
<tr>
<td>IgG reduction (%)</td>
<td>70.63</td>
</tr>
<tr>
<td>IgA reduction (%)</td>
<td>59.00</td>
</tr>
<tr>
<td>IgM reduction (%)</td>
<td>45.80</td>
</tr>
<tr>
<td>treated blood volume (l)</td>
<td>13.92</td>
</tr>
<tr>
<td>treated plasma volume (l)</td>
<td>5.01</td>
</tr>
</tbody>
</table>
Case 1

, 79 yrs

- Myasthenia gravis: initial diagnosis in 2011
- Prior Treatments: Pyridostigmine, Prednisolone
- 04/ 2013: acute generalization, primarily oropharyngeal symptoms, necessity of stomach tube insertion
- Acetylcholine esterase ab > 5nmol/l (very high)

Start of IA treatment April, 08th

- Modalities:
  - Initially 5.4l (x1.5) then 6.4l (x2) plasma volume per treatment
  - 75 -80% reduction of IgG per treatment

Outcome

- significant improvement after 3rd treatment
- removal of stomach tube after 4th treatment
- dismissal after 9 treatments with full restitution
Case 2

16 yrs

- Diagnosis of autoimmune cerebellitis at the age of 13
- Various treatment approaches without success
- Clinical symptoms: major ataxia, cerebellar atrophy, seizures
- Isolation of neuropil antibodies in cerebrospinal fluid, which were undetectable in blood samples

Treatment approach with IA

- 10 treatment sessions, starting November 12th, 2012
- 1-2x plasma volume, mean treatment of 10l blood volume
- Reduction of IgG 70-85%; IgM 50%-70%; IgA 50%.

Outcome

- Neuropil ab could be eluted from columns -> ab were removed
- Slightly reduced frequency of seizures (no further improvement after 6 mon.)
Summary

- Neurological disorders present with a wide variety of (auto)antibodies
- IA effectively removes Ig from large plasma volumes (except for TR-IA)
- IA can be easily applied and is safe (especially compared to PE)
- 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
- Best proof-of-concept data are given for myasthenia gravis and multiple sclerosis
- Prospective, randomized studies are necessary for IA in neurological indications
- We also need to improve our understanding of IA effects apart from ab removal
Thanks for your attention!