Apheresis for the Treatment of IBD

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## History of Apheresis in IBD

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Method</th>
<th>Disease</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Bicks et al.</td>
<td>Centrifugation</td>
<td>CD</td>
<td>4/7</td>
</tr>
<tr>
<td>1995</td>
<td>Sawada et al.</td>
<td>Cellsorba®</td>
<td>UC, CD</td>
<td>UC; 21/25, CD; 16/19</td>
</tr>
<tr>
<td>1996</td>
<td>Rembacken et al.</td>
<td>Adacolumn®</td>
<td>UC, CD</td>
<td>UC; 9/14, CD; 5/6</td>
</tr>
</tbody>
</table>

Widespread use in Japan and EU
Evidence-Based Clinical Efficacy of Cytapheresis in UC

Granulocyte And Monocyte Adsorption Apheresis (GCAP)

- GCAP for steroid-resistant UC by prospective pilot study (Hanai et al: Cin Gastroenterol Hep 1: 28, 2003)
- GCAP is useful as an alternative therapy in steroid-dependent UC (Naganuma et al: Inflamm Bowel Dis 10: 251, 2004)

Leukocytapheresis (LCAP)

- LCAP in UC: A multicenter double-blind prospective case-control study with sham apheresis as placebo treatment (Sawada et al. Am J Gastroenterol 100: 1362, 2005)
Duration: 60 minutes
Flow Rate: 30mL/minutes.
Anticoagulant: Heparin
-Changes in granulocytes function associated with apheresis-

The expression of L-selectin and the adhesion to HUVEC (endothelial cells) were reduced by apheresis procedure.

Subjects: Patients with Rheumatoid Arthritis

Mechanisms of Actions: Immunomodulation 2
Suppression of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-8 produced by blood leucocytes during Adacolumn

Mechanisms of Actions: Immunomodulation 3

Decrease of CD10+ Neutrophils and emergence of CD10- Neutrophils (naive) during Adacolumn therapy

Efficacy of Adacolumn compared to Prednisolone
A Multi-center, Randomized, Clinical Trial in Patients with Active Ulcerative Colitis (UC)

Subjects: 120 with moderately to severely active UC

Randomly divided into Adacolumn group or high dose Prednisolone group

Prednisolone

Adacolumn

1 2 3 4 5 6 7

x1 / week

week 7

overall assessment

Clinical Efficacy of Adacolumn vs Prednisolone

### Types and Frequencies of Adverse Reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Adacolumn (n=59)</th>
<th>Prednisolone (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory and respiratory organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dizziness on standing</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Digestive organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Duodenal perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Reduced bone mass</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Compressed fracture of lumber vertebra</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lipid and protein metabolism disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moon face</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Hypoproteinaemia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dermatological disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total adverse events (Pts)</td>
<td>5/59 (8.5%)</td>
<td>27/59 (45.8%)</td>
</tr>
</tbody>
</table>

GCAP Is Effective for Steroid-Dependent UC

- Remission (58%)
- Response (33%)
- Non-response (8%)

Steroid-Tapering Effect (mg/day)

Efficacy of Intensive Adacolumn Treatment
A Multicenter, Prospective, Randomized, Controlled Trial Between Weekly And Semiweekly Treatment With Adacolumn For Active UC

Weekly Adacolumn (n=45)

1 2 3 4 5 6 7 8 9 10

CAI

Semiweekly Adacolumn (n=52)

1 2 3 4 5

CAI

Sakuraba A, Hibi T et al. 2005 UEGW
An Interim Report of Multicenter, Prospective, Randomized Controlled Trial between Weekly and Semiweekly Treatment with GCAP

**Rate of Inducing Remission**

**Weekly (n=45)**
- Remission: 21 (46.7%)
- Non-response: 19
- Response: 5

**Semiweekly (n=52)**
- Remission: 38 (73.1%)
- Non-response: 11
- Response: 3

**Days for Inducing Remission**
- Weekly: 28.1 days
- Semiweekly: 15.9 days

P=0.012

P=0.0002
Adacolumn apheresis for refractory Crohn's disease
An Open-labeled, Multicenter, Prospective, Unblinded Study

Subjects: 21 CD patients refractory to 5-ASA, steroids etc.
Efficacy: 11/21 (52.4%)
Remission: 6/21 (27.0%)

Efficacy of Adacolumn in Crohn’s disease
An US Pilot, Open-labelled, Multicenter, uncontrolled Trial

Subjects: 15 moderate to severe CD patients refractory to conventional medication
Response: 9/15 (60%)
Remission: 6/15 (40%)

Scheme of Cellsorba Treatment

Anticoagulant

Pump

Blood pump
30 to 50mL/min

Cellsorba™

2 to 3 liter of blood is treated in approx. 1 hour.
# Blood Cell Adsorption Efficiency of Cellsorba

<table>
<thead>
<tr>
<th>Blood Cell Type</th>
<th>Number of cells adsorbed ($\times 10^9$)</th>
<th>Adsorption efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes</td>
<td>11.0</td>
<td>95</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.52</td>
<td>100</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2.0</td>
<td>85</td>
</tr>
<tr>
<td>Platelets</td>
<td>520</td>
<td>55</td>
</tr>
</tbody>
</table>

![Graph showing removal rate over time for different blood cells](image-url)
Mechanism of Action: Immunomodulation 1

Decrease in the number of lymphocytes, T and B cells after Cellsorba therapy

Decrease in the number of CD4+, CD8+ and CD45RO+CD4+ T cells after Cellsorba therapy

Mechanism of Action: Immunomodulation 2

An Increase in the ratio of regulatory T cells/effector T cells

A reduction in the ratio of Th1(IFN-γ)/Th2(IL-4) T cells

Andoh A et al. Therapeutic Apheresis and Dialysis; 2005; 9;270-276.
Efficacy of Cellsorba compared to High-dose Prednisolone
A Multicenter, Prospective, Unblinded Trial

Subjects: 76 Moderate to Severe UC patients

Randomly devided to high-dose Prednisolone group or Cellsorba group

Increase steroid dose 30-80mg/day

High Prednisolone (h-PSL) group

Study starts.

Leukocytapheresis (Cellsorba) group

Study starts.

Steroid (prednisolone)

3.0 ~ 4.0 g/day of SASP or 1.5 ~ 2.0 g/day of 5-ASA

TIME

Cellsorba

Cellsorba is more effective and safer than Prednisolone

A Multicenter, Double Blinded, Prospective Case-Control Study With Cellsorba in Active UC

Improvement Rate (evaluated at week 10)
- Cellsorba (n=10): 80%, 8/10
- Sham (n=9): 33%, 3/9

P < 0.05

Overview of the Pivotal Study of Adacolumn Therapy in US, EU and Japan for Moderate and Severe IBD

- Randomized (2:1 scheme)
- Double-blinded, Placebo (sham)-controlled
- Multi-center (168 UC & 234 CD patients already enrolled in north America), EU and Japan participation
- Treat patients with moderate to severe UC or CD who failed or are intolerant to the standard therapies
- Patients are allowed to be on stable doses of 5-ASA, prednisone (up to 20 mg daily dose), 6-MP and azathioprine while in the study
- Patients will receive 10 treatments within 12 weeks
- Primary endpoint; clinical remission
Pathophysiological Background-Based Treatment of IBD

**Genetic factors**
- Prebiotics
- Probiotics

**Environmental factors**
- Modification of life style (Smoking, Diet, etc)
- Sulfasalazine
- 5-Aminosalicylates

**Intestinal inflammation**
- Corticosteroids
- Surgical Operation

**Immunological abnormalities**

**Enteric flora**
- Asia = Western

**Immunoregulatory Therapies**
- Asia = Western