Asia -
Research needs/gaps - Japan

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Introduction

✓ Therapeutic apheresis has been applied for various autoimmune disorders and others in Japan.

✓ Most of such diseases is often resistant against usual treatment, and the pathomechanism has not been fully elucidated.

✓ The rarity of such diseases has often prevented us from carrying out the randomized controlled trials.
# Apheresis approved in Japan

<table>
<thead>
<tr>
<th>Disease</th>
<th>Maximum no. of sessions</th>
<th>PE</th>
<th>DFPP</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia gravis</td>
<td>7 /month, for 3mos</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Guillain–Barre syndrome</td>
<td>7 /month, for 3mos</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating neuropathy</td>
<td>7 /month, for 3mos</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>7 /month, for 3mos</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Malignant RA</td>
<td>1/week</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>SLE</td>
<td>4 / month</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Pemphigus/ Bullous pemphigoid</td>
<td>2/week, for 3mos</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
</tbody>
</table>
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<tbody>
<tr>
<td>Multiple myeloma</td>
<td>1/w, for 3 mos</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>Macroglobulinemia</td>
<td>1/w, for 3 mos</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>TTP</td>
<td>1/w, 3 mos</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>Blood type– incompatible pregnancy</td>
<td>–</td>
<td>○</td>
<td>○</td>
<td>-</td>
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<tr>
<td>HUS</td>
<td>–</td>
<td>○</td>
<td>○</td>
<td>-</td>
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<tr>
<td>FGS</td>
<td>12, 3 mos</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Familial hypercholesterolemia</td>
<td>1/w</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Arteriosclerosis obliterans</td>
<td>10, for 3 mos</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Hemophilia with inhibitors</td>
<td>–</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
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<tr>
<td>-------------------------------------</td>
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<tr>
<td>Fulminant hepatitis</td>
<td>~10</td>
<td>○</td>
<td>-</td>
<td>○</td>
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<tr>
<td>Drug intoxication</td>
<td>~8</td>
<td>○</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver failure after operation</td>
<td>~7</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>~7</td>
<td>○</td>
<td>○</td>
<td>-</td>
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<tr>
<td>Chronic hepatitis C</td>
<td>~5</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>~4 /before, 2/after</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td></td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>Toxic epidermal necrosis</td>
<td>~8</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>Stevens–Johnson syndrome</td>
<td>~8</td>
<td>○</td>
<td>○</td>
<td>-</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>~6</td>
<td>○</td>
<td>○</td>
<td>-</td>
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</table>
Cytapheresis approved in Japan

- LCAP: UC, RA
- GCAP: UC, Crohn’s disease, Pustular psoriasis
Clinical features of the diseases to be treated by apheresis

- Unknown etiology or pathogenesis.
- Rare diseases.
- Treated with the combination of other agents, such as steroids, immnosuppressants and IVIG.
- Difficult to evaluate the effect.
TIPS to select the treatment

✓ Pathomechanism and the action of treatment
✓ Evidence of efficacy
✓ Adverse effects
✓ Cost
✓ Coverage by National Health Insurance
✓ Maneuver or technical problems
✓ Equipment and facilities
✓ Availability of other treatments
How to establish the evidence of efficacy?

- Theoretical substantiation: elucidation of pathomechanism
- Evidence of efficacy: needs of meta-analysis of RCTs

However....

Unknown etiology or pathogenic substance in most cases

Therefore,....

Needs of RCTs to demonstrate the efficacy
In case of myasthenia gravis

- Pathogenic substance is clear
  - anti-AChR
- Clear effect of apheresis
- No appropriate RCTs
In case of Guillain-Barré syndrome

- Evidence of efficacy of PE by RCTs
  - Guillain-Barré study group. Neurology, 1985

- Then,....

  Pathogenic substance were elucidated; anti-ganglioside antibodies
Difficulties in clinical trials of apheresis

1. **Design of clinical trials**
   - Primary endpoint
   - Randomization
   - Keeping blindness

2. **Other arm of treatment**
   - Placebo (sham PE)?
   - Conventional therapy?
   - IVIG? Combination treatment?

3. **Organization of study**
   - GBS Study Group etc.
   - Costs, Any supports?
APPLICATION OF APHERESIS THERAPY

pathomechanism

- Clear
- Not Clear

Pathogenic substance

- Not Clear

Clear

RCT

evidence

Therapeutic rationale of apheresis
INTRODUCTION & DEVELOPMENT OF CYTAPHERESIS IN JAPAN
CLINICAL APPLICATION OF CYTAPHERESIS

- In the late 1960s  Treatment for leukemia
- 1975  RA, Renal transplantation  Thoracic duct drainage
- Late 1970-1980s  Cytapheresis by centrifuge machine  Chronic progressive MS
Previous studies on lymphocytapheresis demonstrated that only 0.5-1% of total lymphocytes in the human body can be removed.

This raised the question of whether such a small, and transient depletion of lymphocytes can be effective for the treatment of autoimmune diseases.
Thoracic duct lymphocyte drainage in RA

The centrifuge machine had *NOT* come into wide use in Japan.

- **Leukocyte reduction filters** (non-woven fabric) for blood transfusion in the mid 1980s ⇒ **Cellsorba (LCAP)**
- **Leukocyte adosorption by cellrose acetatebeads** ⇒ **Adacolumn (GCAP)**
When Prof Shimoyama first proposed the application of GCAP into patients with UC, his colleagues refused it and returned the patients to home.

They said,

“The treatment is crazy enough to remove WBCs despite of existence of strong inflammation. Our professor should be going mad…!”
Effectiveness in RCTs

- Sawada K et al. Multicenter randomized controlled trial for the treatment of ulcerative colitis with a leukocytapheresis column. Curr Pharm Des 2003


Now, seeking for the mechanism of the action
GCAP & LCAP IN SKIN DISEASES

○ GCAP is effective for neutrophilic dermatosis
  - pyoderma gangrenosum
  - Bechet’s disease
  - Sweet’s disease
  - pustular psoriasis ---- approved
  - psoriatic arthropathy
  - cutaneous allergic vasculitis
  - Reiter’s disease
  - adult onset Still’s disease
  - leg ulcer associated with RA

○ LCAP may be effective for some of above.
GCAP for neutrophilic dermatosis
GCAP or LCAP for Bechet’s disease
PMX treatment (endotoxin adsorption) for acute lung injury
IAPP, PE, and DFPP for NMO
Apheresis for cardiomyopathy
OTHER NEEDS OF RESEARCH

- Apheresis for dementia
- Apheresis for anti-aging
Now Japanese government is setting to reform the medical service for patients with intractable disorders.

This should improve registry systems of each disease and may contribute to the entry of clinical trials.
In Japan, National Health Insurance covers apheresis therapy in the limited diseases and conditions. To obtain the approval, recently there are strong needs to demonstrate the evidence of the efficacy of treatment. Although several uncontrolled trials showed rapid but short-term effects, the rarity of these diseases has often prevented us from carrying out RCTs. Immature registry system and poor strategy for clinical trials in Japan are also obstacles to RCTs. Furthermore, in apheresis therapy, it is also difficult to do sham-treatment and to keep the blindness.