New treatment option for drug refractory cases or crisis stage

Therapeutic Plasmapheresis in autoimmune neurological disorder using Plasma Fractionator Evaflux™

Specification of Plasma Fractionator Evaflux 2A

<table>
<thead>
<tr>
<th>Model</th>
<th>2A10</th>
<th>2A20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollow fiber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Ethylene vinyl alcohol copolymer</td>
<td></td>
</tr>
<tr>
<td>Inner diameter</td>
<td>175 μm</td>
<td></td>
</tr>
<tr>
<td>Wall thickness</td>
<td>65 μm</td>
<td></td>
</tr>
<tr>
<td>Housing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Polypropylene resin</td>
<td></td>
</tr>
<tr>
<td>Membrane surface area</td>
<td>1.0 m²</td>
<td>2.0 m²</td>
</tr>
<tr>
<td>Outer dimension</td>
<td>25.0 x 180.1 mm</td>
<td>37.0 x 280.1 mm</td>
</tr>
<tr>
<td>Printing volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside hollow fibers</td>
<td>Approx. 81 mL</td>
<td>Approx. 108 mL</td>
</tr>
<tr>
<td>Inside hollow fibers</td>
<td>Approx. 82 mL</td>
<td>Approx. 150 mL</td>
</tr>
<tr>
<td>Filled liquid</td>
<td>Sterile water</td>
<td>Sterile water</td>
</tr>
<tr>
<td>Sterilization method</td>
<td>Gamma-ray irradiation</td>
<td>Gamma-ray irradiation</td>
</tr>
</tbody>
</table>

Note
*Please read instructions carefully when using the product.
*Evaflux™ is a trademark of KAWASUMI LABORATORIES, INC.
What is autoimmune neurological disorders?

Autoimmune neurological disorders are believed to be inhibition of tissue due to antigen-specific autoimmune response which targets central nervous system, peripheral nerves and neuromuscular junction.

Clinical conditions are mainly divided into “primarily antibody mediated” and “T-cell mediated”, and other substances like cytokines, chemokines, immune complex and adhesion molecules are also considered to be involved.

Autoantibody targets in autoimmune neurological disorders

<table>
<thead>
<tr>
<th>Autoimmune neurological disorder</th>
<th>Clinical condition</th>
<th>Target</th>
</tr>
</thead>
</table>
| Myasthenia Gravis (MG)           | Autoimmune disease of the neuromuscular junction | 1. anti acetylcholine receptor (AChR) antibody  
2. anti muscle specific receptor tyrosine kinase (MuxR) antibody |
| Guillain–Barré Syndrome (GBS)   | Acute progressive paralyzing illness affecting both motor and sensory peripheral nerves | anti ganglioside antibody |
| Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) | Autoimmune disorder of ganglioside of myelin sheath (spontaneous recovery in most patients) | anti ganglioside antibody |
| Multiple Sclerosis (MS)          | Autoimmune disorder of central nervous system while demyelination involved by cellular immunity | anti myelin basic protein (MBP) antibody, anti myelin oligodendrocyte glycoprotein (MOG) antibody, etc. |
| Neuromyelitis Optica (NMO) / Devic’ syndrome | Autoimmune disorder of optical nerve and spinal cord involved by humoral immunity | anti aquaporin 4 (AQP4) antibody |
| Lambert–Eaton Syndrome (LEMS)    | Autoimmune disorder of the neuromuscular junction and nerve ending | anti voltage-gated calcium channel (VGCC) antibody |

New treatment option: Therapeutic Plasmapheresis in autoimmune neurological disorders

Therapeutic Plasmapheresis is a method for removing pathogenic antibodies from patients’ blood. In autoimmune neurological disorders, it is generally performed when drug therapy is not effective, or in acute exacerbation stage to normalize or to improve the symptoms.

What is the benefit of Therapeutic Plasmapheresis in autoimmune neurological disorders?

- Shorten remission time
- Reduce residual disability and hospital stay
- Reduce dosage (steroid etc.)
- Alleviate adverse side effect
- Apply to drug refractory cases or to patients who can not tolerate
- When immediate effectiveness is needed (e.g. crisis stages)

What is Double / Cascade Filtration?

Double/Cascade Filtration is one of the Therapeutic Plasmapheresis methods.

It’s principle is to selectively deplete a plasma fraction that contains disease associated high molecular weight substances and to reduce or eliminate the requirement for substitution fluid such as albumin.

Fig 1: Principle of Double / Cascade Filtration

(Conceptual diagram was proposed by Prof. Agishi)
Flow Diagram of Double Filtration Plasmapheresis (DFPP)

Flow Diagram of Cascade Filtration (CF)

[ in combination with Centrifugal Cell Separator ]

Performance of Plasma fractionator Evaflux™

- Selective from 4 different pore sizes according to diseases -

Fig 2: Sieving Coefficient of "Evaflux"
(When 1,000 ml of plasma was processed)

Evaflux™ 2A can remove Immunoglobulins while allowing Albumin to be returned

<table>
<thead>
<tr>
<th>Evaflux™ 2A</th>
<th>Alb.</th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.C.</td>
<td>0.62</td>
<td>0.19</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Clinical effects of DFPP: Guillain–Barré Syndrome

Controll study of 12 patients with GBS, who have quadripareisis and unable to stand unaided.


<table>
<thead>
<tr>
<th>Plasmapheresis-pulse therapy group</th>
<th>n=6</th>
<th>Received DFPP followed by pulse therapy (DFPP) 1–3 times every 7 days per patient, using Evoflux 2A. (Pulse therapy) methylprednisolone 1,000mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care group</td>
<td>n=6</td>
<td>Only rehabilitation</td>
</tr>
</tbody>
</table>

**Effect on clinical condition improvement**

In plasmapheresis-pulse therapy group, 5 of 6 patients improved to the point able to walk, although in supportive care group only 1 of 6 patients could.

**Immunological suppression were observed in all the patients with Plasmapheresis-pulse therapy.**

**Fig 3:** Clinical course of the both groups

**Fig 4:** Difference of serum immune factors pre and post DFPP in plasmaphereis-pulse therapy group

- **IgG**
  - Pre: 1000 mg/dl
  - Post: 500 mg/dl
  - P = 0.01

- **lgM**
  - Pre: 50 mg/dl
  - Post: 30 mg/dl
  - P = 0.01

- **C3**
  - Pre: 300 mg/dl
  - Post: 50 mg/dl
  - P = 0.01

- **C4**
  - Pre: 15 mg/dl
  - Post: 5 mg/dl
  - P = 0.01

**Grading Scale for ADL**

- 0: Bedridden
- 1: Able to stand with support
- 2: Able to stand without support but unable to walk
- 3: able to walk with aid
- 4: Unstable walk with effort
- 5: Normal

**Fig 3a:** Plasmapheresis-pulse therapy group

**Fig 3b:** Supportive care group

**Fig 4:** Difference of serum immune factors pre and post DFPP in plasmaphereis-pulse therapy group