Favorable outcome of patients with Kawasaki disease treated with unified protocol with Cyclosporine A as the third line therapy

Hiromichi Hamada, Takafumi Honda, Kumi Yasukawa, Takuya Matsui, and Masaru Terai

Tokyo Women’s Medical University
Yachiyo Medical Center, Chiba, JAPAN

Feb 4th, 2015  IKDS Honolulu, HI
Hiromichi Hamada
Favorable outcome of patients with Kawasaki disease treated with unified protocol with Cyclosporine A as the third line therapy

FINANCIAL DISCLOSURE:
No relevant financial relationship exists

UNLABELED/UNAPPROVED USES DISCLOSURE:
Cyclosporine A
26691 KD patients were reported between 2011-2012 (two years) in Japan. Among them, 24346 patients received IVIG, and 4150 (17.0%) did not respond it. 

\[
\frac{4150}{24346} = 17.0\%
\]

Cyclosporine A for Kawasaki disease


*Pediatr Infect Dis J* 2011;30:871-6

Hypothesis of CsA as a targeting drug

Patients with KD → SNPs are found in *ITPKC* and *CASP3*

⇒ Function of *ITPKC*, *Caspase3* is down → excess inflammatory cytokines

Two enzyme suppress Ca2+/NFAT Pathway

- ITPKC
- Caspase3


⇒ Normal function of ITPKC, Caspase3 is to suppress excessive activation of immune cells
Aim

We examine result of the unified protocol using CsA as a third line therapy for IVIG non-responders between 2008-2014.
Patients

KD patients who admitted in our hospital and received initial treatment were included for analysis.


n= 441, male / female=252 / 189

Age; 1month to 11years, median= 2y3mo,
Protocol

2008-10

24Hrs 24Hrs 24Hrs 14-21days

IVIG ① 2g/kg IVIG ② 2g/kg IVIG ③ CsA 4mg/kg/d, oral

CsA; Cyclosporine A

Acetylsaritilic acid 50mg/kg/d

2011-14

3 or 5 days 24Hrs

IVIG ① 2g/kg IVIG ② 2g/kg CsA 5mg/kg/d, oral IVIG ③ (option)

(Suzuki H, et al. Ped Infect Dis J;2011)
Result; IVIG response

1st IVIG: 80%
2nd IVIG: 15%
3rd line therapy: 5%

n=441

n=23
21: CsA
2: 3rd IVIG
Case #1; 3ys old: CAL-

<table>
<thead>
<tr>
<th>Day of illness</th>
<th>3</th>
<th>4</th>
<th>9</th>
<th>11</th>
<th>14</th>
<th>18</th>
<th>22</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms 5/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>10.0</td>
<td>9.2</td>
<td>14.1</td>
<td>4.5</td>
<td>1.9</td>
<td>0.5</td>
<td>0.2</td>
<td>0.03</td>
</tr>
<tr>
<td>CsA trough concentration (ng/mL)</td>
<td>72</td>
<td>80</td>
<td>63</td>
<td>55</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylsaritilic acid 50mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA 4mg/kg/d oral for 21 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case #6; 1 y old: CAL-IVIG

<table>
<thead>
<tr>
<th>Day of Illness</th>
<th>PLT (X10e4/ul)</th>
<th>CRP (mg/dl)</th>
<th>Na (mEq/l)</th>
<th>ALB (g/dl)</th>
<th>IgG (mg/dl)</th>
<th>IL-6 (pg/ml)</th>
<th>sIL-2R (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>16.6</td>
<td>132</td>
<td>3.9</td>
<td>3.9</td>
<td>452</td>
<td>300</td>
<td>863</td>
</tr>
<tr>
<td>5</td>
<td>9.6</td>
<td>130</td>
<td>2.5</td>
<td>2.5</td>
<td>2212</td>
<td>129</td>
<td>319</td>
</tr>
<tr>
<td>6</td>
<td>11.8</td>
<td>131</td>
<td>2.2</td>
<td>2.2</td>
<td>3629</td>
<td>166</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>135</td>
<td>2.5</td>
<td>2.5</td>
<td>1858</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>21-23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>133</td>
<td></td>
</tr>
</tbody>
</table>

**IVIG**

**CsA 147259 (ng/ml)**

**14 days**
CsA for 14-21 days as a third line therapy

★ 78% of patients got afebrile within 5 days on CsA.

★ There are no serious adverse effects by CsA in KD patients.

Modification of the protocol: short-term CsA treatment (2011-2014)

11 patients received CsA treatment according this protocol.
Case #11: 1y old; CAL-

Day of illness

<table>
<thead>
<tr>
<th></th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38.9°C</td>
</tr>
<tr>
<td></td>
<td>37.0°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>200</td>
<td>160</td>
<td>160</td>
<td>140</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>3.7 mg/dL</td>
<td>5.1</td>
<td>5.3</td>
<td>1.3</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>ALB</td>
<td>4.2 g/dL</td>
<td>2.9</td>
<td>2.6</td>
<td>3.1</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>CAL</td>
<td>#5 1.6mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>#6 1.9mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CsA</td>
<td>5 mg/k/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>3179</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4311</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3days

IgG 3179
Case #13: 3 yrs old; CAL+

Day of illness:

- **BT**: 37.0°C (37.6°C)
- **HR**:
  - 3 days: 180
  - 4 days: 140
  - 6 days: 130
  - 8 days: 120
  - 13 days: 100
  - 14 days: 100

- **CRP**:
  - 3 days: 8.3 mg/dL
  - 4 days: 9.7
  - 6 days: 4.3
  - 8 days: 3.8
  - 13 days: 7.6
  - 14 days: 4.3

- **ALB**:
  - 3 days: 3.8 g/dL
  - 4 days: 2.4
  - 6 days: 2.4
  - 8 days: 2.6
  - 13 days: 2.7
  - 14 days: 2.6

- **CAL**:
  - 5 days: 2.1 mm
  - 6 days: 1.2 mm

- **IVIG**
  - Days 3-8

**Patient Management**:
- **CsA 5mg/kg/d** administered from 13 days onwards.
- **IgG 2764** indicated.
11 cases with short-term CsA treatment

Data before CsA treatment

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>1st IVIG day</th>
<th>2nd IVIG day</th>
<th>Data after 2nd IVIG (before CsA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-62</td>
<td>3-6</td>
<td>5-8</td>
<td>WBC (X1000/uL) CRP (mg/dL) ALB (g/dL) Na (mEq/L)</td>
</tr>
<tr>
<td>42</td>
<td>4</td>
<td>6</td>
<td>15.8 ± 10.2 ± 2.6 ± 134 ±</td>
</tr>
<tr>
<td>(Median, range)</td>
<td>(Day of illness)</td>
<td>(Mean ± SD)</td>
<td>4.0 5.1 0.4 1.8</td>
</tr>
</tbody>
</table>

CsA: Cyclosporin A
### Result 1

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; IVIG day</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; IVIG day</th>
<th>CsA start day</th>
<th>No of pts getting afebrile</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; IVIG day</th>
<th>No of pts getting afebrile</th>
<th>Day of getting afebrile</th>
<th>No of pts with CAL</th>
<th>Hospital length of stay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>13</td>
<td>11</td>
<td>11</td>
<td>1/11</td>
<td>18</td>
</tr>
<tr>
<td>Range</td>
<td>3–6</td>
<td>5–8</td>
<td>6–9</td>
<td>10–17</td>
<td>10–27</td>
<td>11–30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAL: Coronary artery lesion  
CsA: Cyclosporine A  
Day: Day of illness
# 11 cases with short-term CsA treatment

## Result 2

<table>
<thead>
<tr>
<th></th>
<th>IgG conc. after 2(^{nd}) IVIG</th>
<th>CsA start day</th>
<th>CsA conc. (Trough, 3(^{rd}) day)</th>
<th>IgG conc. before 3(^{rd}) IVIG</th>
<th>3(^{rd}) IVIG day (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*3797 mg/dL</td>
<td>8</td>
<td>125 mg/dL</td>
<td>*2816 mg/dL</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>**828 mg/dL</td>
<td>6-9</td>
<td>55-194 mg/dL</td>
<td>**242 mg/dL</td>
<td>10-17</td>
</tr>
</tbody>
</table>

Conc.: concentration  
* mean  
** SD
Coronary complications

CAL: 5 / 441 = 1.13% (Giant AN: 0)
Summary

441 KD patients were treated on unified protocol with oral CsA following 3\textsuperscript{rd} IVIG as the third line therapy.

There were no serious adverse events associated with CsA.

Occurrence of CAL was 1.1\%. Maximum coronary diameter of the 5 patients with CAL was 5.5mm.

When patients did not get afebrile with CsA, 3\textsuperscript{rd} IVIG was effective in these patients. CsA might affect on immune and inflammatory systems and modify IVIG responsiveness.

146: H.Suzuki; Tomorrow Poster
High risk KD patients (*Risk score > 5)

IVIG + CsA + Aspirin

1st line

IVIG + Aspirin

Hata A, Tomorrow Lunch Symposium

Multicenter RCT under regulation of Good Clinical Practice (GCP), approved by PMDA (Japan FDA)

*Kobayashi, et al. Circulation 2006*
Acknowledgement

Prof. Masaru Terai, MD

Chiba

Clinical Research Team

Pediatric Care Team

Character TYMC Greens!!