MANAGEMENT OF IVIG NON-RESPONDERS IN KAWASAKI DISEASE

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CONTENT

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Background

- IVIG non-responders: persistent or recrudescent fever ≥36-48 hours after the completion of the initial IVIG infusion
- The incidence: 10 – 20%
- IVIG non-responders: increased risk of CAAs
- Optimal therapy: controversial
• Additional IVIG treatment
• High-dose intravenous pulse methylprednisolone (IVMP)
• TNF-α blockade
• Cyclosporine A
• IL-1 blockade
• Methotrexate
• Anti-CD20
IVIG retreatment

Recommend IVIG 2g/kg (Level C)

### Steroids

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of IVIG non-responder</th>
<th>Study design</th>
<th>Study population</th>
<th>Treatment protocol</th>
<th>Number of patients with CAAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright 1996</td>
<td>4</td>
<td>Case series</td>
<td>KD patients with IVIG non-response after 2 IVIG doses</td>
<td>IVMP (30 mg/kg/day for 1-3 days)</td>
<td>4/4 (100%)</td>
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<tr>
<td>Dale 2000</td>
<td>7</td>
<td>Case series</td>
<td>KD patients with IVIG non-response after 2 IVIG doses</td>
<td>Oral PRED (2mg/kg/day for 2 weeks)</td>
<td>5/7 (71.4%)</td>
</tr>
<tr>
<td>Hashino 2001</td>
<td>17 / 262 (7%)</td>
<td>Randomized controlled trial</td>
<td>KD patients with IVIG non-response after 2 IVIG doses</td>
<td>IVMP (20 mg/kg/day for 3 days) [n=9] versus 3rd IVIG infusion (1g/kg) [n=8]</td>
<td>7/9 (77.8%) versus 5/8 (62.5%) P=NS</td>
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</tbody>
</table>
## Steroids

### Studies about steroids as second line treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miura(^5^7) 2005</td>
<td>22 / 169 (13%)</td>
<td>Randomized controlled trial</td>
<td>KD patients with non-response to initial IVIG infusion ((\geq 48) h after IVIG)</td>
</tr>
<tr>
<td>Furukawa(^4^5) 2008</td>
<td>63 / 411 (13%)</td>
<td>Retrospective, multicenter, cohort study</td>
<td>KD patients with non-response to initial IVIG infusion ((&gt;36) h after IVIG). IVIG was only given to patients whose families refused IVMP.</td>
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<tr>
<td>Ogata(^5^8) 2009</td>
<td>27 / 164 (16%)</td>
<td>Prospective, comparative study between 2 different centers</td>
<td>KD patients aged 2 months – 10 years with IVIG non-response ((&gt;36-48) h after initial IVIG infusion)</td>
</tr>
</tbody>
</table>
Steroids

- as second-line treatment (i.e., in patients after initial IVIG failure)
- or as third-line treatment (i.e., in patients after non-response to repeated IVIG infusions)
- faster resolution of fever
- similar rate of CAAs compared to IVIG retreatment
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Description</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns</td>
<td>2008</td>
<td>Multicenter, randomized controlled trial (pilot trial)</td>
<td>KD patients (initial IVIG within 14 days with non-response 48h-7 days after the IVIG infusion.)</td>
<td>Infliximab (5 mg/kg) [n=12] versus 2nd IVIG (2 g/kg) [n=11]</td>
<td>Cessation of fever (&lt;24h): 92% versus 67%. No differences in laboratory variables, fever or coronary artery outcome. Infliximab was safe and well-tolerated.</td>
</tr>
<tr>
<td>Son</td>
<td>2011</td>
<td>2-center retrospective review</td>
<td>KD patients with IVIG non-response</td>
<td>Infliximab (5 mg/kg) [n=20] versus 2nd IVIG (2 g/kg) [n=86]</td>
<td>CAAs: 35% versus 34% (P=.91) Fever: 8 versus 10 days (P=.028) Hospitalization: 5.5 versus 6 days (P=.033) Adverse events: 0% versus 2.3% (P=1.00)</td>
</tr>
<tr>
<td>Morii</td>
<td>2012</td>
<td>Open label trial</td>
<td>KD patients with IVIG non-response (≥48h after initial IVIG infusion)</td>
<td>Infliximab (5 mg/kg)</td>
<td>Rapid improvement of inflammatory symptoms and markers. No adverse events. Two patients were refractory to infliximab (and underwent plasma exchange therapy).</td>
</tr>
</tbody>
</table>
TNF-α blockade

- TNF-α: key pro-inflammatory cytokine
- Elevated plasma level of TNF-α: increased risk of CAA
- TNF blockade: infliximab and etanercept
- Infliximab (5 mg/kg): Rapid improvement of inflammatory symptoms and markers, no adverse side effects
Cyclosporine A

  - Pilot study (329 KD pts)
  - 28 Japanese patients with IVIG non-response
  - cyclosporin A dose: 4-8 mg/kg/day
  - 18 pts: afebrile within 3 days (64.3%), 4pts within 4-5 days

- Tremoulet et al (2012): case series of 10 KD pts
  - rapid defervescence and resolution of inflammation

IL-1 blockade

- Case reports
- In a mouse model for KD: Lee et al showed that IL-1β is indeed critically involved in the coronary arteritis and that the coronary lesions can be prevented by IL-1RA treatment

Lee YH, Schulte DJ, Shimada K et al. IL-1 beta is Crucial for Induction of Coronary Artery Inflammation in a Mouse Model of Kawasaki Disease. Circulation 2012 February 2
Methotrexate

- Case series
- In a subsequent trial by Lee et al:
  - low-dose oral methotrexate therapy (10 mg/m², once weekly until CRP levels normalized)
  - 17 IVIG non-responsive patients
  - Methotrexate: prompt resolution of fever and rapid improvement of inflammatory parameters

Anti CD20 treatment

- Sauvaget et al: a single case of a child with KD who was successfully treated with rituximab (15 mg/kg/day)

Other treatment

- **Plasma exchange**

- **Ulinastatin:**
  - inhibits neutrophil elastase and prostaglandin H2 synthase
  - Kanai et al:
    - ulinastatin plus IVIG and aspirin (n=369) compared with patients treated with conventional therapy (n=1178).
      - ulinastatin was associated with fewer patients requiring additional rescue therapy (13% vs. 22%; P<0.001) and a reduction in CAA formation (3% vs. 7%; P=0.01)

  - used in Japan as an adjunctive therapy for KD patients

Conclusion

- IVIG retreatment: recommend
- Other drugs: IVMP, infliximab and anti-IL-1 treatment
- Need more researchs
REFERENCES


Thanks for your attention