EVIDENCE BASED MEDICINE

MANAGEMENT OF IVIG NON-RESPONDERS IN KAWASAKI DISEASE

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2. IVIG RETREATMENT
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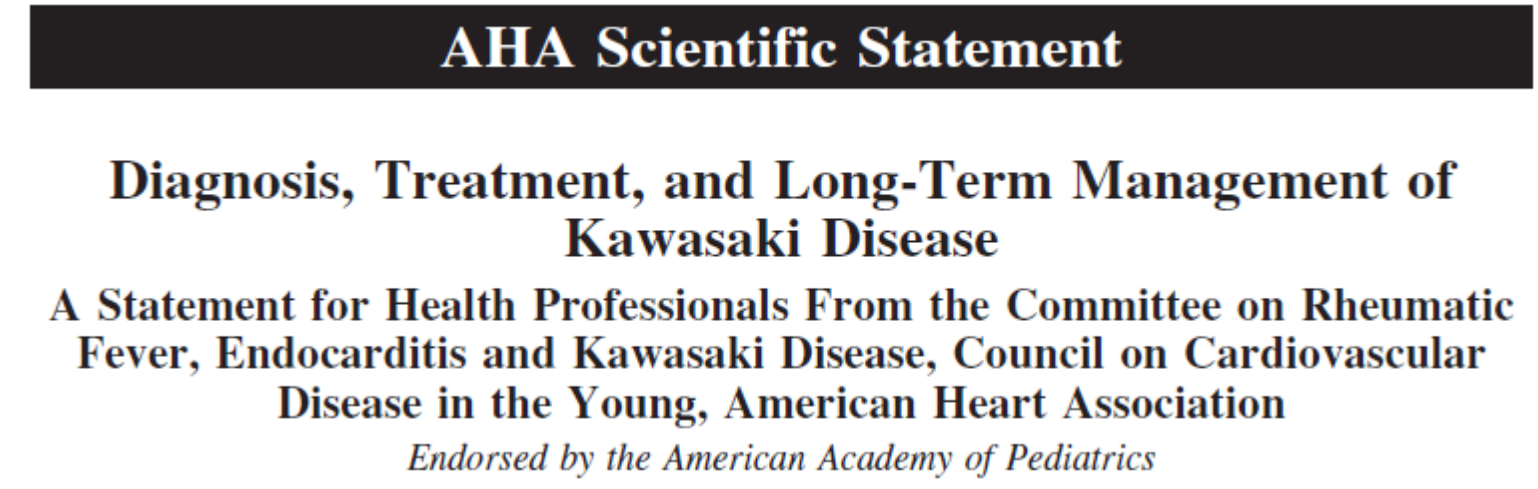
Background

- 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



AHA Scientific Statement

Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease

A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association

Endorsed by the American Academy of Pediatrics

- Recommend IVIG 2g/kg (Level C)

Newburger JW, Takahashi M, Gerber MA et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004;114:1708-33.

Steroids

Study	No. of IVIG non-responder	Study design	Study population	Treatment protocol	Number of patients with CAAs
Studies about steroids as third line treatment					
Wright[54] 1996	4	Case series	KD patients with IVIG non-response after 2 IVIG doses	IVMP (30 mg/kg/day for 1-3 days)	4/4 (100%)
Dale[55] 2000	7	Case series	KD patients with IVIG non-response after 2 IVIG doses	Oral PRED (2mg/kg/day for 2 weeks)	5/7 (71.4%)
Hashino[56] 2001	17 / 262 (7%)	Randomized controlled trial	KD patients with IVIG non-response after 2 IVIG doses	IVMP (20 mg/kg/day for 3 days) [n=9] *versus* 3rd IVIG infusion (1g/kg) [n=8]	7/9 (77.8%) *versus* 5/8 (62.5%) *P*=NS

Steroids

Studies about steroids as second line treatment

Miura[57] 2005	22 / 169 (13%)	Randomized controlled trial	KD patients with non-response to initial IVIG infusion (≥48 h after IVIG)	IVMP (30 mg/kg/day for 3 days) [n=11] *versus* 2nd IVIG infusion (2 g/kg over 24h) [n=11]	3/11 (27.3%) *versus* 2/11 (18.2%) *P*=NS
Furukawa[45] 2008	63 / 411 (13%)	Retrospective, multicenter, cohort study	KD patients with non-response to initial IVIG infusion (>36 h after IVIG). IVIG was only given to patients whose families refused IVMP.	IVMP (30 mg/kg/day for 3 days), followed by PRED (1mg/kg/day) tapered over 7 days [n=44] *versus* 2nd IVIG infusion (1-2 g/kg) [n=19]	2/19 (10.5%) *versus* 5/44 (11.4%) *P*=NS
Ogata[58] 2009	27 / 164 (16%)	Prospective, comparative study between 2 different centers	KD patients aged 2 months – 10 years with IVIG non-response (>36-48 h after initial IVIG infusion)	IVMP (30 mg/kg/day for 3 days) [n=13] *versus* 2nd IVIG infusion (2g/kg) [n=14]	0/13 (0%) *versus* 3/14 (21.4%) *P*=NS

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

TNF-α blockade

Burns[67] 2008	24	Multicenter, randomized controlled trial (pilot trial)	KD patients (initial IVIG within 14 days) with non-response 48h-7 days after the IVIG infusion.	Infliximab (5 mg/kg) [n=12] *versus* 2nd IVIG (2 g/kg) [n=11]	Cessation of fever (<24h): 92% *versus* 67%. No differences in laboratory variables, fever or coronary artery outcome. Infliximab was safe and well tolerated.
Son[68] 2011	106 / 641 (16.5%)	2-center retrospective review	KD patients with IVIG non-response	Infliximab (5 mg/kg) [n=20] *versus* 2nd IVIG (2 g/kg) [n=86)	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)
Mori[69] 2012	20	Open label trial	KD patients with IVIG non-response (≥48h after initial IVIG infusion)	Infliximab (5 mg/kg)	Rapid improvement of inflammatory symptoms and markers. No adverse events. Two patients were refractory to infliximab (and underwent plasma exchange therapy).

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

- Suzuki et al (2011) :
  - 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

Suzuki H, Terai M, Hamada H et al. Cyclosporin A treatment for Kawasaki disease refractory to initial and additional intravenous immunoglobulin. Pediatr Infect Dis J 2011;30:871-6.
Tremoulet AH, Pancoast P, Franco A et al. Calcineurin Inhibitor Treatment of Intravenous Immunoglobulin- Resistant Kawasaki Disease. J Pediatr 2012

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-1beta 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/m^2, once weekly until CRP levels normalized)
  - 17 IVIG non-responsive patients
  - Methotrexate: prompt resolution of fever and rapid improvement of inflammatory parameters

Lee TJ, Kim KH, Chun JK, Kim DS. Low-dose methotrexate therapy for intravenous immunoglobulinresistant Kawasaki disease. Yonsei Med J 2008;49:714-8

Anti CD20 treatment

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

Sauvaget E, Bonello B, David M, Chabrol B, Dubus JC, Bosdure E. Resistant Kawasaki Disease Treated with Anti-CD20. J Pediatr 2012

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

Kanai T, Ishiwata T, Kobayashi T et al. Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study. Circulation 2011;124:2822-8.

Conclusion

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

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Thanks for your attention