Kawasaki disease: Studies on etiology, treatment and long-term follow-up
Tacke, C.E.A.

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Chapter 3

THE MANAGEMENT OF ACUTE AND REFRACTORY KAWASAKI DISEASE

C.E. Tacke
D. Burgner
I.M. Kuipers
T.W. Kuijpers

SUMMARY
Acute Kawasaki disease (KD) is treated with high-dose intravenous immunoglobulin (IVIG), which is proven to decrease the incidence of coronary artery aneurysms (CAAs) from 25% to less than 5%. Aspirin is also given, although the evidence base is less secure. There is increasing evidence for steroid therapy as adjunctive primary therapy with IVIG, especially in Asian children. Approximately 10 to 30% of patients fail to respond to the initial IVIG and are at increased risk of CAAs. The optimal treatment for IVIG non-responsive KD remains controversial. Management options include further dose(s) of IVIG, corticosteroids, TNF-α blockade, cyclosporin A, anti-IL-1, and anti-CD20 therapy. In this article, we review the current evidence for treatment of acute KD and discuss options for IVIG non-responders.
INTRODUCTION
Kawasaki disease (KD) is an acute systemic pediatric vasculitis that was first described in 1967 in Japan. Up to 25% of untreated KD patients develop coronary artery aneurysms (CAAs), which may lead to ischemic heart disease, myocardial infarction and sudden death at a young age. Kawasaki disease is the most common cause of acquired heart disease in children in developed countries. Children younger than 5 years of age are mainly affected and the disease is predominant in males. KD is clinically characterized by persistent fever, a lack of response to antibiotics and a constellation of other features, which together form the cardinal diagnostic criteria: bilateral conjunctival injection, rash, erythema of the lips and oral mucosa, cervical lymphadenopathy, and changes of the extremities.

The etiology of KD remains unclear, despite four decades of research. The consensus is that KD reflects an abnormal inflammatory response to one or more unknown infectious triggers in genetically susceptible individuals. A genetic predisposition to KD susceptibility is suggested by the striking difference in incidence between children of Asian (113 – 240 per 100,000 children <5 years of age) and European descent (8-17 per 100,000 children <5 years of age), which is maintained following migration of Asians to countries with a lower incidence. In addition, the incidence of KD is increased in siblings of KD patients and in children born to parents with a history of KD. The clinical and epidemiological features of KD support an infectious cause, including the presence of self-limiting symptoms that usually do not recur, elevated inflammatory parameters, the age distribution with a predominance in young children, seasonal variation, and the occurrence of epidemics. However, efforts to identify a single unifying infectious agent have failed. Autopsy studies of KD patients have demonstrated a systemic inflammatory process involving many tissues and organs, but most strikingly affecting the coronary arteries.

Standard treatment of the acute KD phase is based on trial evidence and consists of high-dose intravenous immunoglobulin (IVIG), given within 10 days of the onset of fever. This reduces the incidence of CAAs to about 5% and shortens the duration of fever. Aspirin is also given, although the dosage regimen varies between centers and the evidence base for its use is less secure. However, up to a third of patients will have persistent or recrudescent fever after a single dose of IVIG and these patients are at higher risk for the development of CAAs. The optimal therapy for IVIG non-responders remains controversial. Here we review the treatment of the acute KD phase, and focus on management options for IVIG non-responsive patients.

INITIAL TREATMENT OF ACUTE KAWASAKI DISEASE

IVIG
IVIG is a polyclonal IgG preparation purified from pooled plasma from healthy blood donors. In addition to its use in Kawasaki disease, IVIG is used in primary and secondary immune
deficiencies, and several other autoimmune and systemic inflammatory diseases\textsuperscript{11}. Successful treatment of KD patients with IVIG was first described in 1984 by Furusho \textit{et al.}\textsuperscript{12}, and was subsequently confirmed by other studies\textsuperscript{13-17} (Table 1). Treatment with IVIG reduces the incidence of CAAs, and results in a shorter duration of fever and leads to improvement in inflammatory parameters. Patients should be treated with IVIG (2 g/kg) given by a single large infusion over 10-12 hours, rather than multiple infusions (400 mg/kg/day for 4-5 consecutive days), as was previously advocated\textsuperscript{16}. However a single large IVIG infusion is a considerable

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study population</th>
<th>Treatment protocol</th>
<th>Patients with CAAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Subacute</td>
<td>Convalescent</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>15% versus 8% (n=40)</td>
<td>versus 42% versus 31% (n=45)</td>
</tr>
<tr>
<td>Furusho\textsuperscript{12} 1984</td>
<td>85</td>
<td>Patients with KD, ≤7 days after disease onset</td>
<td>IVIG (400 mg/kg/day for 4 days) + aspirin</td>
<td>P&lt;0.01 (&lt;30 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>versus aspirin (n=45)</td>
<td>(30-60 days)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>8% versus 23% (n=75)</td>
<td>versus 18% (2 weeks)</td>
</tr>
<tr>
<td>Newburger\textsuperscript{13} 1986</td>
<td>153</td>
<td>Patients with KD, ≤10 days after disease onset</td>
<td>IVIG (400 mg/kg/day for 4 days) + aspirin</td>
<td>P=0.01 (30 days)</td>
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<td>versus aspirin (n=78)</td>
<td>P=0.005 (7 weeks)</td>
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<td></td>
<td>13% versus 31% (n=69)</td>
<td>versus 5% (4 weeks)</td>
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<tr>
<td>Nagashima\textsuperscript{14} 1987</td>
<td>136</td>
<td>Patients with KD, ≤10 days after disease onset and no CAA at enrolment.</td>
<td>IVIG (400 mg/kg/day for 3 days) + aspirin</td>
<td>P&lt;0.05 (7 weeks)</td>
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<td></td>
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<td></td>
<td>versus aspirin (n=67)</td>
<td>(4 weeks)</td>
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<td></td>
<td></td>
<td></td>
<td>5% versus 9% (n=22)</td>
<td>versus 0% (2 weeks)</td>
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<tr>
<td>Barron\textsuperscript{15} 1990</td>
<td>44</td>
<td>Patients with KD, ≤7 days after disease onset</td>
<td>IVIG (400 mg/kg/day for 4 days) + aspirin</td>
<td>P=NS (1 year)</td>
</tr>
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<td></td>
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<td></td>
<td>versus IVIG (1 g/kg in 1 infusion) + aspirin (n=22)</td>
<td>(1 year)</td>
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<td></td>
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<td>9.1% versus 4.6% (n=276)</td>
<td>versus 3.9% (2 weeks)</td>
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<tr>
<td>Newburger\textsuperscript{16} 1991</td>
<td>549</td>
<td>Patients with KD, ≤10 days after disease onset</td>
<td>IVIG (400 mg/kg/day for 4 days) + aspirin</td>
<td>P=0.042 (7 weeks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>versus IVIG (2 g/kg in 1 infusion) + aspirin (n=273)</td>
<td>(2 weeks)</td>
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<td></td>
<td></td>
<td></td>
<td>13% (A) versus 5% (B)</td>
<td>versus 8% (C)</td>
</tr>
<tr>
<td>Morikawa\textsuperscript{17} 1994</td>
<td>451</td>
<td>Patients with KD, ≤9 days after disease onset</td>
<td>A: IVIG (200 mg/kg in 5 doses) + aspirin</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
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<td>versus aspirin (n=147)</td>
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<td></td>
<td>B: IVIG (400 mg/kg in 5 doses) + aspirin</td>
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<td></td>
<td></td>
<td></td>
<td>versus aspirin (n=152)</td>
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<td></td>
<td></td>
<td>C: IVIG, another brand (200 mg/kg in 5 doses) + aspirin</td>
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</tbody>
</table>

**Table 1. Randomized trials evaluating the efficacy of IVIG as primary treatment for patients with Kawasaki disease.**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study population</th>
<th>Treatment protocol</th>
<th>Patients with CAAs</th>
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<tbody>
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<td>Newburger\textsuperscript{18} 1991</td>
<td>549</td>
<td>Patients with KD, ≤10 days after disease onset</td>
<td>IVIG (400 mg/kg/day for 4 days) + aspirin</td>
<td>P=0.042 (7 weeks)</td>
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<td></td>
<td>versus IVIG (2 g/kg in 1 infusion) + aspirin (n=273)</td>
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<td></td>
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<td>versus 8% (C)</td>
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<td>Morikawa\textsuperscript{17} 1994</td>
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<td>versus aspirin (n=147)</td>
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<td></td>
<td>B: IVIG (400 mg/kg in 5 doses) + aspirin</td>
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<td>versus aspirin (n=152)</td>
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<td></td>
<td></td>
<td>C: IVIG, another brand (200 mg/kg in 5 doses) + aspirin</td>
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</tr>
</tbody>
</table>

**Abbreviations:** CAA=coronary artery aneurysm; IVIG=intravenous immunoglobulin; NS=not significant; RCT=randomized controlled trial.
oncotic load, and in patients with pancarditis and compromised cardiac function, a slower infusion may be necessary; expert advice should be sought. When possible, treatment should be started within 10 days of disease onset\textsuperscript{18}. The CAA rate in patients appropriately treated with IVIG is approximately 5\%\textsuperscript{16}. Although a study by Tse \textit{et al}. suggested that treatment with IVIG on or before 5 days of fever may result in better coronary outcomes\textsuperscript{19}, most studies showed no evidence that early treatment within 5 days after the onset of illness has greater efficacy in preventing CAAs than treatment on day 5-9\textsuperscript{20,21}. Early treatment may result in an increased need for IVIG retreatment\textsuperscript{20,21}. Although differences exist between brands and lots of IVIG, most studies failed to find a significant difference between IVIG products\textsuperscript{22-23}. The mechanism of action of IVIG is still not understood, but it appears to have generalized anti-inflammatory effects. Increased levels of pro-inflammatory cytokines have been reported during the acute KD phase, including TNF-\(\alpha\), IL-1 and IL-6\textsuperscript{25-27}. The elevated cytokine levels normalize rapidly after IVIG therapy, suggesting that these pro-inflammatory mediators play a major role in the KD pathogenesis and that reducing circulating and local cytokines may have major therapeutic benefit in KD. In addition to modulation of inflammatory cytokine production, other proposed mechanisms of IVIG include neutralization of bacterial superantigens or other causative agents, inhibition of endothelial cell proliferation and activation, augmentation of regulatory T-cell activity, balancing Th1/Th2 response, reduction of NO production by neutrophils and reducing antibody-producing B-cells\textsuperscript{28}.

\textbf{Aspirin}

Aspirin has been used in the treatment of KD patients for many years because of its anti-inflammatory (at higher doses) and antithrombotic properties (at lower doses). The probable efficacy of high-dose aspirin (80-180 mg/kg/day) in the acute KD phase in reducing the incidence of CAAs was suggested in an early study by Koren \textit{et al.}\textsuperscript{29}. Although no prospective study has confirmed that aspirin reduces the incidence of CAAs, it has become part of the standard treatment in KD\textsuperscript{30-33}. Aspirin is usually given at anti-inflammatory doses during the acute phase, but controversy remains regarding the exact dose. In the USA and Europe, aspirin at high-dose (80-100 mg/kg/day in four doses) is most widely recommended, whereas concern about hepatic toxicity led to the use at a more moderate dose (30-50 mg/kg/day, ordinarily in three doses) in Japan\textsuperscript{2}. In Australia a lower antithrombotic dose (3-5 mg/kg/day) is often commenced from the onset of disease. Practices regarding the duration of high-dose aspirin administration also vary between centers. Some clinicians continue high-dose aspirin until day 14 of illness; others reduce the dose after the child has been afebrile for 48-72 hours. In general, the dose is reduced (to 3-5 mg/kg per day) after the acute phase and continued until there is no evidence on echocardiography of coronary artery involvement at 6-8 weeks after the disease onset. Aspirin is continued until complete resolution of CAAs has been established, or indefinitely
in those patients who developed persistent CAAs. In patients with severe coronary artery pathology, more intense anticoagulant treatment is needed.

**Steroids**

Corticosteroids suppress immune responses and have potent anti-inflammatory effects. They are widely used as first-line therapy in many vasculitides. It is therefore plausible that steroids would be beneficial in the acute management of KD. However, the administration of steroids has been much debated since an early study by Kato *et al* in the pre-IVIG era (1979) that suggested an increased risk of CAA formation in patients primarily treated with steroids. Eleven of the 17 patients (65%) treated with oral prednisolone developed CAAs. Interestingly, in the same study none of the 7 patients treated with prednisolone plus aspirin developed CAAs. The study of Kato *et al* was a non-randomized and uncontrolled study performed in a small number of patients. Subsequent studies evaluating the initial treatment of KD patients with steroids showed no effect or a possible beneficial effect (Table 2).

The Pediatric Heart Network evaluated whether the addition of intravenous methylprednisolone (IVMP) to the initial therapy for KD reduced the CAA risk in a large, multicenter, double-blind, placebo-controlled trial of 199 patients with KD. Patients were randomized to receive a single pulsed dose of IVMP (30 mg/kg over 2 to 3 hours) or placebo, in addition to standard treatment with IVIG and aspirin. The coronary z-scores at week 1 and 5, numbers of days of fever and rates of retreatment with IVIG were similar between the two study groups, suggesting no overall benefit in unselected US patients with KD. In post hoc analyses, the coronary artery outcomes of children with persistent fever who received IVIG retreatment were better in the IVMP subgroup. The authors concluded that the addition of IVMP to conventional therapy is not indicated for routine treatment of KD, but may be beneficial for patients at high-risk of IVIG non-response and CAAs.

Kobayashi *et al* recently published results from the RAISE study, a multicenter trial in Japan in 242 KD patients at high risk for IVIG non-response and coronary artery involvement (using a Japanese-derived risk stratification system for likely IVIG non-response that was developed by the same authors). They assessed whether addition of prednisolone to the standard initial treatment with IVIG and aspirin reduced the incidence of CAAs. Participants were randomized to receive IVIG (2 g/kg infusion in 24 hours) with aspirin (30 mg/kg/day), or the same regimen with the addition of prednisolone. Prednisolone was given at 2 mg/kg/day in three divided doses given by intravenous injection for 5 days. If fever had resolved, the prednisolone dose was reduced and given orally. This study showed that addition of prednisolone to the standard regimen improves coronary artery outcome in the primary treatment of high-risk KD patients (3% vs. 23% during the study period; *P* < 0.0001 and 3% vs. 13% at week 4; *P* = 0.014). In addition, the IVIG plus prednisolone group had more rapid fever resolution (median duration of fever 1 vs. 2 days; *P* < 0.0001) and the need for additional
### Table 2. Studies evaluating the efficacy of steroids as primary treatment for patients with Kawasaki disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study design + population</th>
<th>Treatment protocol *</th>
<th>IVIG</th>
<th>Aspirin</th>
<th>Steroids</th>
<th>Patients with CAAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Subacute</td>
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<td></td>
<td></td>
<td></td>
<td>Convalescent</td>
</tr>
<tr>
<td>Sundel 34 2003</td>
<td>39</td>
<td>RCT in KD patients with ≤10 days of fever and no CAA at baseline</td>
<td>IVMP + IVIG (n=21) versus IVIG (n=18)</td>
<td>2 g/kg in 1 dose (over 10 hours)</td>
<td>20-25 mg/kg/day</td>
<td>30 mg/kg/day in 1 dose</td>
<td>24% vs. 14% P=NS (2 weeks) 5% vs. 6% P=NS (6 weeks)</td>
</tr>
<tr>
<td>Okada 35 2003</td>
<td>32</td>
<td>RCT in KD patients with ≤10 days of fever</td>
<td>IVIG + prednisolone (n=14) versus IVIG (n=18)</td>
<td>1 g/kg/day (2 days)</td>
<td>30 mg/kg/day</td>
<td>2 mg/kg/day, in 3 doses until fever resolved</td>
<td>0% vs. 0% P=NS -</td>
</tr>
<tr>
<td>Jibiki 36 2004</td>
<td>46</td>
<td>Prospective case-control study in KD patients with no CAA at baseline (historical control group)</td>
<td>DEX + IVG (n=46) versus IVG (n=46)</td>
<td>2 g/kg (over 4-5 days)</td>
<td>30 mg/kg/day</td>
<td>Heparin (10 U/kg/day during DEX)</td>
<td>0.30 mg/kg/day for 3 days 4% vs. 4% P=NS (2 weeks) -</td>
</tr>
<tr>
<td>Inoue 37 2006</td>
<td>178</td>
<td>RCT in KD patients with 4-10 days of fever and no CAA at baseline</td>
<td>PRED + IVG (n=90) versus IVG (n=88)</td>
<td>1 g/kg for 2 days (over 12 hours)</td>
<td>30 mg/kg/day</td>
<td>2 mg/kg/day in 3 doses (first IV, then oral until CRP normalized)</td>
<td>2% vs. 11% P=0.017 (until 1 month) 0% vs. 3% P=0.119 (at 1 month)</td>
</tr>
<tr>
<td>Newburger 38 2007</td>
<td>199</td>
<td>RCT in KD patients with 4-10 days of fever</td>
<td>IVMP + IVG (n=101) versus Placebo + IVG (n=98)</td>
<td>2 g/kg/day in 1 dose (over 2-3 hours) 80-100 mg/kg/day</td>
<td>30 mg/kg/day in 1 dose</td>
<td>30% vs. 30% P=0.10 (1 week) 16% vs. 19% P=0.70 (5 weeks)</td>
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<tr>
<td>Studies in high-risk KD patients</td>
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<tr>
<td>Okada 39 2009</td>
<td>94</td>
<td>Prospective case-control study in KD patients at high-risk for IVIG non-response (no CAA at baseline). Historical control group.</td>
<td>IVMP + IVG (n=62) versus IVG (n=32)</td>
<td>2 g/kg in 1 dose (over 24 hours)</td>
<td>30 mg/kg/day</td>
<td>30 mg/kg/day in 1 dose</td>
<td>3% vs. 25% P=0.002 -</td>
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<tr>
<td>Ogata 40 2012</td>
<td>48</td>
<td>RCT in KD patients at high-risk for IVIG non-response and no CAA at baseline</td>
<td>IVG (n=26) versus IVMP + IVG (n=22)</td>
<td>2 g/kg in 1 dose (over 24 hours)</td>
<td>30 mg/kg/day</td>
<td>30 mg/kg/day in 1 dose</td>
<td>9% vs. 39% P=0.04 (1 month) -</td>
</tr>
<tr>
<td>Kobayashi 41 2012</td>
<td>248</td>
<td>RCT in KD patients at high-risk for IVIG non-response with &lt;9 days of fever and no CAA at baseline</td>
<td>PRED + IVG (n=125) versus IVG (n=123)</td>
<td>2 g/kg in 1 dose (over 24 hours)</td>
<td>30 mg/kg/day</td>
<td>2 mg/kg/day in 3 doses (IV for 5 days, than oral)</td>
<td>3% vs. 23% P&lt;0.0001 3% vs. 13% P=0.014 (4 weeks)</td>
</tr>
</tbody>
</table>

* Information about the administration of aspirin is not recorded in this column.

Abbreviations: CAA=coronary artery aneurysm; DEX=dexamethasone; IV=intravenous; IVIG=intravenous immunoglobulins; IVMP=intravenous methylprednisolone; KD=Kawasaki disease; NS=not significant; PRED=prednisolone; RCT=randomized controlled trial.
rescue therapy was lower (13% vs. 40%; $P<0.001$). The number of serious adverse events was similar in the groups.

Discordance between the US and Japanese trials may partly be due to differences in the study populations and treatment regimens (i.e. a single dose versus a prolonged course of steroids). Taking into account the results of the studies of Okada et al. and Ogata et al. that showed a positive effect of a single dose of steroids on the coronary outcomes (Table 2), the differences in study populations of both trials seem to be the most important explanation. The RAISE study was performed in children of Japanese origin who were at high risk for IVIG non-response and CAAs, based on the Kobayashi risk score. The Kobayashi risk score does not accurately predict IVIG non-response in the non-Japanese population, with a very low sensitivity of 33% and specificity of 87%.

Further study examining the addition of steroids to the conventional primary treatment in a different or mixed ethnic population, as well as in other Asian cohorts of high-risk KD patients seems to be warranted, but only when patients at high-risk of IVIG non-response can be discriminated reproducibly from the majority of low-risk patients. To avoid overtreatment with steroids, the development of more widely applicable risk parameters for CAA formation is therefore required.

**MANAGEMENT OF IVIG NON-RESPONDERS**

The majority of patients treated with IVIG and aspirin respond promptly within 48h. However, a subgroup of patients fails to have a good clinical response to a single infusion of IVIG and has persistent or recrudescent fever ≥36-48 hours after the completion of the initial IVIG infusion. The incidence of IVIG-non-response varies in most centers ranging between 10-20% but can be as high as 38% as reported in a US cohort in 2006. Various risk factors for IVIG-non-response have been described, including early treatment before day 5, male gender, laboratory parameters (e.g. increased CRP, low hemoglobin, low albumin and low sodium) and recurrent KD. IVIG non-responders are at increased risk of CAAs.

A large study of 15,940 Japanese patients reported in IVIG non-responders a significantly higher risk of CAAs (odds ratio: 10.38; 95%CI: 6.98 – 15.45) and of giant CAAs (odds ratio: 54.06; 95%CI: 12.84 – 227.65).

The optimal therapy for IVIG non-responders remains controversial as controlled trial data are lacking, and therefore, the agent used as additional therapy varies between centers and investigators. Additional IVIG treatments, high-dose intravenous pulse methylprednisolone (IVMP), TNF-α blockade, cyclosporine A, IL-1 blockade, methotrexate, anti-CD20, and other treatments have been used for KD patients with initial failure to respond to IVIG.

**IVIG retreatment**

A second dose of IVIG is recommended by most experts, including the American Heart Association consensus guidelines, for KD patients with an incomplete response to the first
dose of IVIG. In up to 80% of these patients, a second dose is effective in controlling disease activity. In a multicenter survey by Burns et al, IVIG non-responders retreated with 1 g/kg infusion had a significantly greater likelihood of developing CAA, compared with those retreated with infusions of 2 g/kg (4 out of 7 patients (57.1%) versus 1 of 17 patients (5.9%); \( P=0.014 \)). On the basis of these results, a dose of 2 g/kg is recommended instead of a lower dose of 1 g/kg for IVIG retreatment.

**Steroids**

Only small and largely uncontrolled studies have been performed on the efficacy of steroids in IVIG non-responders. Overall, these studies reported a faster resolution of fever, but

<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>
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<tr>
<td>Wright</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>
</tr>
<tr>
<td>Dale</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</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) vs 3rd IVIG infusion (1g/kg)</td>
<td>7/9 (77.8%) vs 5/8 (62.5%)</td>
</tr>
</tbody>
</table>

**Studies about steroids as second line treatment**

<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>Miura</td>
<td>22 / 169 (13%)</td>
<td>Randomized controlled trial</td>
<td>KD patients with non-response to initial IVIG infusion (&gt;48h after IVIG)</td>
<td>IVMP (30 mg/kg/day for 3 days) vs 2nd IVIG infusion (2 g/kg over 24h)</td>
<td>3/11 (27.3%) vs 2/11 (18.2%)</td>
</tr>
<tr>
<td>Furukawa</td>
<td>63 / 411 (13%)</td>
<td>Retrospective, multicenter, cohort study</td>
<td>KD patients with non-response to initial IVIG infusion (&gt;36h after IVIG). IVIG was only given to patients whose families refused IVMP.</td>
<td>IVMP (30 mg/kg/day for 3 days), followed by PRED (1mg/kg/day) tapered over 7 days vs 2nd IVIG infusion (1-2 g/kg)</td>
<td>2/19 (10.5%) vs S/44 (11.4%)</td>
</tr>
<tr>
<td>Ogata</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;36-48h after initial IVIG infusion)</td>
<td>IVMP (30 mg/kg/day for 3 days) vs 2nd IVIG infusion (2g/kg)</td>
<td>0/13 (0%) vs 3/14 (21.4%)</td>
</tr>
</tbody>
</table>

Abbreviations: CAA=coronary artery aneurysm; IVIG=intravenous immunoglobulins; IVMP=intravenous methylprednisolone; KD=Kawasaki disease; NS=not significant; PRED=prednisolone.
a similar rate of CAs in patients with IVIG failure treated with steroids compared to IVIG re-
treatment. The studies performed can be separated in studies about 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) (Table 3).

Hashino et al performed a randomized controlled trial examining steroids as third-line treat-
ment. The study was performed in 17 KD patients who were non-responsive to 2 doses of
IVIG (13.4% in a total of 262 patients who were treated with IVIG). Patients were randomized
to receive a 3-day course of IVMP (30 mg/kg once daily) or a third IVIG infusion (1 g/kg).
No difference in rate of CAs was observed, but the steroid group had a shorter duration
of high fever (1.4±0.7 days vs. 4.8±3.4 days; \( P<0.05 \)). In addition, the medical costs for the
patients treated with IVMP pulse therapy were significantly lower than those for the IVIG
retreatment group.

In 2005, Miura et al performed the first small randomized controlled trial about IVIG as
second-line treatment. A second IVIG infusion (n=11) was compared with IVMP treatment
(n=11) in patients with initial IVIG failure, but the study was halted prematurely because of
adverse effects of IVMP. Although the adverse events were transient, sinus bradycardia (82% vs.
18%; \( P=0.01 \)) and hyperglycemia (55% vs. 0%; \( P=0.01 \)) occurred more frequently in the
IVMP group. Two other studies comparing IVMP versus IVIG as second-line treatment for
KD did not report a comparison of the side effects between both groups. The studies
observed a shorter duration of fever in the IVMP group, but no difference in the CAA rate. In
the IVMP group, significantly lower medical costs were reported. The recommendation of
the American Heart Association is to restrict steroid treatment to children in whom two or
more IVIG infusions have been ineffective.

TNF-α blockade

TNF-α is a key pro-inflammatory cytokine and circulating levels of TNF-α are markedly el-
evated in acute KD patients. The plasma level of TNF-α is correlated with an increased
risk of CAA development and TNF-α polymorphism may be associated with disease suscepti-
bility. In a well-characterized animal model for coronary vasculitis, intraperitoneal injection
of Lactobacillus casei cell wall extract results in coronary inflammation. In this model, which
is the most frequently used to study KD pathogenesis, blocking TNF-α activity resulted
in complete protection from coronary artery inflammation. In addition, TNF-α receptor
I-deficient mice did not develop coronary arteritis, indicating that the TNF-α receptor pathway is responsible for signaling TNF-α-mediated functions leading to coronary artery
inflammation in this model. These observations suggest a key role for TNF-α in KD etiology
and a potential role for TNF-α blockers in treatment of KD.

In human studies of TNF blockade in KD, data from 2 biologics have been reported: infliximab
and etanercept. Infliximab is a chimeric mouse-human monoclonal antibody that binds
specifically to human TNF-α. Etanercept is a dimeric fusion protein consisting of the ligand-
Table 4. Studies evaluating TNF-α blockade as treatment for IVIG non-responsive patients with Kawasaki disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of IVIG non-responders</th>
<th>Study design</th>
<th>Study population</th>
<th>Treatment protocol</th>
<th>Main study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns66</td>
<td>2005 17</td>
<td>Case series</td>
<td>Patients with refractory KD after at least two doses of IVIG</td>
<td>Infliximab (5 mg/kg) [n=15] or Infliximab (10 mg/kg) [n=2]</td>
<td>Defervescence in 13/16 patients, and decrease of CRP levels. No Infusion reactions or complications.</td>
</tr>
<tr>
<td>Burns67</td>
<td>2008 24</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>Son68</td>
<td>2011 106 / 641 (16.5%)</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>CAA: 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=.100)</td>
</tr>
<tr>
<td>Mori69</td>
<td>2012 20</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>

Abbreviations: CAA=coronary artery aneurysm; IVIG=intravenous immunoglobulins; KD=Kawasaki disease.

The binding portion of the human p75 TNF receptor linked to the Fc portion of human IgG1. The beneficial effect of infliximab has been suggested in individual cases, and in larger non-randomized studies of patients with IVIG non-response (Table 4). In a retrospective study, Burns et al reported rapid clinical improvement in 13 of the 16 IVIG non-responders treated with a single infusion of infliximab. Cessation of fever and lowering of CRP levels was observed following infliximab treatment. These authors subsequently conducted a clinical trial in 24 children to assess the safety, tolerability and pharmacokinetics of infliximab (5 mg/kg) versus a second IVIG infusion (2 g/kg) in KD patients non-responsive to the initial IVIG infusion. Both infliximab and IVIG retreatment were safe and well tolerated. A retrospective study by Son et al in 2011 compared the efficacy and safety of a second IVIG infusion (n = 86; at 2 g/kg) with infliximab (n = 20; at 5 mg/kg) for patients with initial IVIG non-response. Patients who were first retreated with infliximab had faster resolution of fever (median 8 versus 10 days; P=0.028) and fewer days of hospitalization (median 5.5 versus 6 days; P=0.040), compared with IVIG retreatment, but coronary artery dimensions and adverse events were similar. The power of this study was limited. Recently, results of an open-label case series
Part II     Treatment

of infliximab treatment (5 mg/kg) in 20 KD patients with initial IVIG failure were published. This study also demonstrated rapid improvement of clinical symptoms and normalization of inflammatory markers in the majority of patients (90%). Echocardiography revealed that the increased echogenicity or mild dilatation observed in all patients regressed to normal size within the convalescent phase. Only one patient had CAAs, which had completely normalized 1 year later.

In another study about the efficacy of infliximab for IVIG non-responders and the dynamic changes of cytokines during infliximab treatment, a concern was raised that TNF blockade may suppress systemic inflammation, but not local vasculitis. Serum levels of pro-inflammatory cytokines decreased dramatically in response to infliximab treatment, but VEGF and local proteins that trigger inflammation remained high – including molecules in so-called damage-associated molecular pattern pathways, including MRP8/MRP14 and S100A12. These proteins are involved in local pro-inflammatory mechanisms of the vessel wall and may play an important role in the development of CAAs. Future prospective, randomized clinical trials (RCTs) are needed to establish the role and efficacy of anti-TNF-α therapy in IVIG non-responsive patients.

Of note, results of two multicenter RCTs to assess the efficacy of infliximab, as well as of etanercept, in reducing the IVIG non-response and CAA rate during initial treatment of KD are expected shortly. A preceding small pilot trial in 15 patients suggested etanercept (0.4–0.8 mg/kg over a 2-week period) to be safe and well tolerated as adjunctive treatment for the first IVIG infusion. None of the patients required retreatment or rescue therapy.

Cyclosporin A

In KD management, cyclosporin A may be an effective treatment option because it is a negative regulator of the calcineurin/nuclear factor of activated T-cells (NFAT) pathway and therefore suppresses T-cell activity. There is increasing evidence from a variety of studies that T-cells are likely to be central to KD vascular pathogenesis. In T-cells inositol 1,4,5-trisphosphate (IP3), released by stimulation of the T-cell receptor complex, increases intracellular calcium. The increased levels of calcium activate calcineurin, which leads to nuclear translocation of NFAT, and transcription of IL-2. Inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) acts as a negative regulator of T-cell activation by reducing IP3. In 2008, Onouchi et al. reported, in a genome-wide linkage study in Japanese and US children, on a functional single nucleotide polymorphism (SNP) in the ITPKC gene (rs28493229) on chromosome 19q13.2 that was significantly associated with KD susceptibility and formation of CAAs. The C risk allele of this SNP reduces splicing activity of the ITPKC mRNA, which in turn results in increased signaling through the calcineurin/NFAT pathway and cell activation, and may contribute to immune hyperactivity in KD. In a large case-control genome wide association study (GWAS) in 2173 KD patients and 9383 controls, Khor et al. recently confirmed the previ-
ous findings of a genetic association in the region of the *ITPKC* gene. Collectively, these findings would support a potential role for cyclosporin A in the management of KD. Clinical experience to date is limited, but the beneficial effect of cyclosporin A in a single IVIG non-responsive KD patient has been reported. Suzuki *et al* evaluated oral cyclosporin A treatment in a pilot study of 28 Japanese patients with non-response to the initial and additional IVIG infusion. The initial dose of cyclosporin A was 4-8 mg/kg/day (in two doses), and the dose was adjusted to 4-8 mg/kg/day to maintain a trough level of 60 to 200 ng/mL. Treatment was continued until the patients became afebrile and their CRP level decreased to a negative value (<0.3 mg/dL). Eighteen patients became afebrile within 3 days (64.3%), and 4 within 4-5 days. The remaining 6 patients had persistent or recrudescent fever at least 5 days after cyclosporin A treatment. Four patients developed CAAs, 2 before and 2 after the start of cyclosporin A treatment. There were no serious adverse effects, which was important because of a reported case of fatality in a boy with severe therapy-resistant KD, who was treated with cyclosporin A. A recent case series of 10 American KD patients on calcineurin/NFAT inhibitors supported the findings on safety and efficacy of Suzuki *et al*.

These patients had failed to respond to multiple therapies, but treatment with cyclosporin A (*n* = 9) or tacrolimus (*n* = 1) resulted in rapid defervescence and resolution of inflammation in all patients.

**Anti-IL-1 treatment**

IL-1 is another pro-inflammatory cytokine that is considered as the gatekeeper of inflammation. The IL-1 family consists of three proteins: IL-1α, IL-1β and IL-1 receptor antagonist (IL-1RA). IL-1β is the predominant species of human IL-1. This protein becomes bioactive when the pro-IL-1β is cleaved by caspase-1 to IL-1β. Caspase-1 is activated by the action of a large intracellular complex known as the inflammasome. IL-1 signaling is mediated through binding to the IL-1 receptor. IL-1 RA can competitively bind the IL-1 receptor and prevent signaling.

Several studies reported elevated levels of IL-1β in acute KD patients, and it has been shown that administration of IVIG is associated with a decrease in the IL-1β secretion and an increase of IL-1RA production. In addition, in patients with KD, IL-1β polymorphisms are associated with an increased IL-1β production and IVIG non-response. Gene expression patterns have shown that acute KD was characterized by increased relative abundance of gene transcripts associated with innate immunity and pro-inflammatory processes, including several genes in the IL-1 pathway. In addition, comparison of the transcript abundance profiles of IVIG responsive and non-responsive subjects revealed that transcripts of the IL-1 pathway genes were more abundant in the non-responders. This highlights the potential importance of the IL-1 signaling pathway in KD and suggests a potential role for anti-IL-1 therapy in IVIG non-responders. A variety of biologic agents target the IL-1 pathway,
including anakinra (recombinant human IL-1RA), and canakinumab (recombinant human anti-IL-1β monoclonal antibody).

We recently reported for the first time the beneficial use of anakinra in a severely affected KD patient with extensive coronary artery pathology. The boy was successfully treated with anakinra for 7 days after non-response to IVIG and IVMP, and for another period of 6 weeks when he developed recurrent disease. His coronary artery lesions normalized within the following 6 months.

In a mouse model for KD with *L. casei* wall extract, 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. In addition, there was a trend toward a more effective inhibition of the incidence of CAA formation and inflammation severity score in these mice, as well as lower myocarditis score in the IL-1RA treated mice (anakinra), compared with the anti-TNF group (infliximab). Anti-IL-1 treatment may provide new therapeutic strategies to prevent coronary lesions in KD.

Canakinumab is another biologic agent that targets the IL-1 pathway. It is a human monoclonal antibody that specifically inhibits IL-1β signaling. Canakinumab has the advantage of its long half-life (26 days), compared to anakinra (4-6 h). Further research regarding the efficacy of anti-IL-1 treatment, including anakinra or canakinumab, is warranted.

**Methotrexate**

The efficacy of methotrexate treatment has been suggested in an individual case report and in a case series of 4 KD patients. In a subsequent trial by Lee *et al*, low-dose oral methotrexate therapy (10 mg/m², once weekly until CRP levels normalized) was administered in 17 IVIG non-responsive patients. Methotrexate resulted in prompt resolution of fever and rapid improvement of inflammatory parameters. No patient had recurrent fever after cessation of methotrexate therapy. The small sample size in this single-centre study provided insufficient power to assess coronary artery outcomes and adverse effects.

**Anti-CD20 treatment**

A marked increase of circulating B-cells with the production of cytotoxic immunoglobulins directed against endothelial cells has been documented in patients with KD, and B-cell suppression therefore seems to be a potential treatment option. Rituximab, a chimeric anti-CD20 monoclonal antibody, is a biologic agent that is specifically directed against the CD20 antigen present on B-cells and induces B-cell immunosuppression. Sauvaget *et al* recently reported a single case of a child with KD who was successfully treated with rituximab (15 mg/kg/day). This boy had not responded to 3 infusions of IVIG retreatment and steroid therapy. Rituximab resulted in a cessation of fever, decrease in acute phase reactants and an improvement of the coronary pathology. The treatment regimen was well tolerated, and additional IVIG was given to decrease the infectious risk associated with rituximab. However,
the additional costs associated with repeated IVIG may make this therapy unsuitable for widespread use though.

Other treatments

Plasma exchange therapy has been reported as an effective alternative therapy in IVIG non-responsive KD patients to reduce the incidence of CAA"s. However, plasma exchange therapy is not generally recommended because of its medical costs and possible risks, including hypotension, electrolyte abnormality, bleeding, allergy, and infection. Several studies have indicated that markedly activated neutrophils or elevated levels of neutrophil elastase are involved in IVIG failure and CAA formation. Urinary trypsin inhibitor (ulinastatin) is a glycoprotein derived from human urine, which inhibits neutrophil elastase and prostaglandin H2 synthase at messenger RNA level. Ulinastatin is considered to be a reasonable treatment option for KD patients, and has been used in Japan as an adjunctive therapy for KD patients. The only study that showed a decrease in the occurrence of CAA"s is a recent retrospective study performed by Kanai et al. These authors evaluated whether addition of ulinastatin to the initial KD treatment improved coronary artery outcomes. Patients who had initially been treated with ulinastatin plus IVIG and aspirin (n=369) were compared with patients who had been treated with conventional therapy (n=1178). The authors showed that 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).

Therapy of early cardiovascular complications

In patients without CAA"s or with transient dilatations, antiplatelet therapy is discontinued after the sub-acute stage at 6-8 weeks, if echocardiography is normal at this time. Long-term treatment with aspirin is recommended for patients with persistent coronary artery lesions because of an increased risk of intracoronary thrombosis due to an abnormal blood flow in the aneurysms. Low-dose aspirin (3-5 mg/kg/day) is the mainstay for children with persistent small-to–medium-sized aneurysms (3-6 mm). For patients with larger (>6 mm) or giant (>8 mm) aneurysms, adjunctive anticoagulant treatment is recommended and expert advice should be sought.

One study has reported a significantly lower incidence of myocardial infarction in patients with giant CAA"s treated with a combination of low-dose aspirin and warfarin (n = 19; target INR: 1.5-2.5 IU) than in those treated with aspirin alone (n=49). Sudden death occurred in 7 patients (14%) taking aspirin alone, but in none of the patients taking the combination therapy, although this difference was not statistically significant. Although oral warfarin is currently recommended for long-term anticoagulant treatment, the use of subcutaneous low-molecular-weight heparin has been suggested as a reliable alternative. A retrospective study by Manlhiot et al found that, compared with oral warfarin, the use of low-molecular-weight heparin was associated with a similar frequency of thrombosis, lower rates of sub-
supra-therapeutic coagulation and a reduction in major bleeding episodes. Interestingly, the maximum CAA z-scores diminished over time for patients on low-molecular-weight heparin but not for those on warfarin, although the mechanism is unknown. Larger RCTs may be warranted.

The platelet fibrinogen receptor glycoprotein (GP) IIb/IIIa plays an important role in platelet thrombus formation. Abciximab is a blocking monoclonal antibody acting as GP IIb/IIIa inhibitor associated with the reduction of thrombotic complications and vascular remodeling in adults with acute coronary syndromes. Administration of abciximab has been proposed for KD patients with large CAAs, after rapid regression of large CAAs was observed in a single patient who had been treated with abciximab. Williams et al. subsequently reported that patients with large CAAs (>5mm) treated with abciximab in addition to standard therapy (n = 6) demonstrated greater regression in CAA diameter at early follow-up (4-6 months) than patients who received standard therapy alone (n = 9); percentage decrease 41±19% vs. 17±27%, p=0.003. In the abciximab group, 13 of the 19 (68%) CAAs resolved at early follow-up compared with 7 of 19 (35%) in the standard therapy group. McCandless et al. retrospectively analyzed long-term follow-up data on the changes in diameters of large CAAs (diameter >5 mm or z-score >10) in patients receiving both abciximab and standard therapy (n = 11), and compared these changes to those of a similar group receiving standard therapy alone (n = 7). The change in CAA z-score compared with baseline was similar in the two groups at 1 year, but at 3-5 years of follow-up the abciximab group had a greater decrease in the CAA z-score (-14.0 ± 4.0 vs. -8.2 ± 5.9; P=0.04). Abciximab treatment may be associated with vascular remodeling in patients with large aneurysms. Prospective large clinical trials are needed to establish the effectiveness of abciximab.

**Expert commentary and five-year view**

Standard therapy for patients with KD is well established and consists of a single infusion of high-dose IVIG (2 g/kg) and aspirin, although the optimal dose regimen for aspirin is unclear and there is limited evidence for its efficacy in acute KD. For 10-20% of KD patients who do not respond to the initial IVIG infusion, we recommend a second dose (2 g/kg) of IVIG because this has been shown to be safe and effective in controlling disease activity in the majority (up to 80%) of these patients. IVMP, infliximab and anti-IL-1 treatment should be reserved for the small number of patients non-responsive to repeated IVIG infusions, because limited data are currently available regarding the safety and efficacy of these treatments. In our view, anti-IL-1 treatment may provide a promising treatment option, with the potential to prevent coronary artery lesions, although the evidence to date is at the level of a case report and clinical experience is limited. Larger, multicenter clinical trials in different ethnic populations are warranted to identify the best treatment regimen for IVIG non-responders.

Over the next 5 years, we anticipate major developments in the genetic field, resulting in identification of the genes influencing disease susceptibility and therapy efficacy in KD pa-
tients. This may result in a better identification of patients at high risk for IVIG non-response and CAA development, and may allow improvement of therapy, including the possibility of targeted steroid therapy in high-risk patients. In addition, we believe that the use of biologic agents, including anakinra or infliximab, in treatment of IVIG non-responsive patients will increase significantly over the next 5 years.
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