A Practical Approach to Refractory Kawasaki Disease

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Conflict of interest statement:
CR: No disclosures or conflicts of interest
PB: Declares receiving consultancy fees and institutional grants from Novartis, SOBI, and Roche.

Abstract

Kawasaki disease (KD) is a medium vessel vasculitis and is the most common cause of acquired heart disease in childhood. If left untreated, KD leads to coronary artery aneurysms in 15-25% of patients; mortality rate in the UK is currently 0.4%. As such, KD is an important preventable cause of heart disease in the young. The aetiology of KD remains unknown, but most likely it represents an aberrant inflammatory host response to one or more as yet unidentified immunological trigger(s) in genetically predisposed individuals. The purpose of this article is not to provide an exhaustive review of KD, since many others have already done that; rather, we provide practical guidance to the clinical approach to refractory KD. Only brief background on the pathogenesis and epidemiology of KD, and emerging newer clinical trials is provided, to place our clinical approach in context.

Keywords: Kawasaki disease; IVIG resistance; coronary artery aneurysm; glucocorticoids

Background

KD is a medium vessel vasculitis with a predilection to the coronary arteries and is the most common cause of acquired heart disease in childhood. It is an important preventable cause of heart disease in the young. There is a worldwide distribution, but it is most common in Japanese and children of African descent in the UK. There is some seasonality as it tends to peak during winter and spring and has a male pre-dominance of 1.5:1. In the UK, the current incidence is 4.55 per 100 000 children under 5 years (1).

The aetiology of KD remains unknown, but most likely it represents an aberrant inflammatory host response to one or more as yet unidentified immunological triggers in genetically predisposed individuals. The seasonality and cluster of cases has led to a hunt for infectious agents but to date, no single pathogen has been confirmed. A genetic contribution is suspected given the much higher risk of the disease in Asian children, particularly the Japanese and Koreans, which persists when patients of these ethnicities migrate to other countries. This genetic risk is not monogenic in nature, however; polymorphisms in several genes have been associated with risk of developing KD, non-response to primary treatment, or risk of coronary artery aneurysm (CAA). Genetic markers have not provided any diagnostic test, however, and the diagnosis remains clinical.

If left untreated, KD leads to coronary artery aneurysms in 15-25% of patients; mortality rate in the UK is currently 0.4%; coronary vasculitis and late sequelae are the main prognostic determinants (2). The first-line treatment, which includes a single high dose of intravenous immunoglobulin (IVIG) and aspirin reduces the risk of developing a coronary artery aneurysm or coronary dilation from 25–30% to as low as 4% (3, 4). More recently, however, higher CAA rates have been observed despite timely use of IVIG, resulting in a reappraisal of IVIG/aspirin as primary treatment for all cases (4).

Diagnosis

There is no diagnostic test for KD and the diagnosis rests on combinations of clinical criteria for typical (complete) cases, and lab findings for incomplete cases. According to the American Heart Association, diagnosis is made with a fever duration of 5 days or more, plus four of five of the listed items (Table 1). The Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) experts acknowledged that the requirement for fever $\geqslant$5 days may lead to delayed treatment; thus diagnosis may be made earlier than day 5 of fever, if fever plus $\geqslant$4 principal clinical features are present (4). Additionally, many patients may have some but not all of the clinical features of KD. These patients are still at risk of CAA. Diagnosis of these 'incomplete KD' cases depends on a high level of suspicion in children who present with some of the KD features and evidence of systemic inflammation (such as elevated C reactive protein, erythrocyte sedimentation rate, or leucocytosis). It is important to remember that the features of KD may present sequentially and may thus not all be present at presentation (4).

Primary treatment: IVIG and aspirin

Early recognition and treatment of KD with IVIG and aspirin has been shown to reduce the occurrence of CAA. Therefore, IVIG and aspirin should be started as soon as a patient is diagnosed with KD. Two g/kg of IVIG is the optimal dose. The need for moderately high dose aspirin (30-50 mg/kg/day, in 3-4 divided doses) has recently been questioned; antiplatelet doses of 3-5 mg/kg/day from the outset may be just as effective. Persistent CAA necessitate continuation of low-dose aspirin long term (2). Even if CAA resolve, it is increasingly recognised that coronary artery function remains abnormal, although the long-term prognostic significance of this is uncertain.

What is refractory Kawasaki disease?

There is no standard definition of refractory KD, although there are varying definitions of resistance to intravenous immunoglobin (IVIG) cited in international guidelines and used in clinical trials, most commonly defined as failure of fever to resolve within 36- 48 hours of first IVIG dose. We regard the definition of refractory KD to be somewhat broader than that applied to IVIG resistance. We define refractory KD as: failure of resolution of **systemic inflammation** within 48 hours of **primary treatment**. The term systemic inflammation requires some qualification; we no longer rely solely on resolution of fever, in the KD literature referred to as defervescence, as a metric of therapeutic success. Defervescence is a somewhat confusing term, and we suggest it is best avoided because it does not specify that resolution of fever should also be accompanied by rapid normalisation of systemic markers of inflammation (including rapid fall C reactive protein, CRP). Secondly, primary treatment no longer solely refers to just IVIG plus aspirin; increasing use of glucocorticoids as first-line treatment, particularly for high-risk cases, now mandates that refractory cases may also include those with lack of adequate response to glucocorticoids as well as IVIG/aspirin. For these reasons, in this article and in our clinical practice, we suggest that refractory KD is not synonymous with IVIG resistance, although refractory KD clearly would include patients defined as having IVIG resistance.

Gauging success of primary treatment

Rapidly switching off the inflammatory process reduces the risk of CAA (4). Close monitoring of patients is therefore critical in the first days of treatment, taking into account temperature, clinical symptoms, and acute phase reactants particularly CRP which we measure daily in the first 5 days of treatment. The therapeutic target in KD is "zero fever, zero CRP". This means that 48 hours following treatment, patients should be afebrile **and** CRP should be either normal (<10 mg/L) or at least halving every 24 hours, since the half-life of CRP when hepatic production is halted is approximately 18 hours. Failure to satisfy both these requirements in our practice indicates refractory KD and is an indication for rescue treatment. At this stage, the non-mutually exclusive options include:

- Second dose of IVIG
- Glucocorticoids
- Anti-TNF (infliximab)
- IL-1 blockade (anakinra)
- Ciclosporin

Other treatments described have included methotrexate, cyclophosphamide, or plasma exchange; none of these latter have gained particular traction, and are non-evidence based and hence will not be considered further. In addition, consideration must be given to anti-coagulation, anti-aggregation, and thrombolytic treatments, beyond the scope of this review, but reviewed extensively elsewhere (4).

Treatment of Refractory KD

Second IVIG dose

The SHARE guidance recommends the use of a second dose of IVIG to be left at the discretion of the treating physician (4). In patients who have shown some but not complete response, we suggest that

a second dose of IVIG is given at the same time as commencing steroids if they have not already been commenced for signs of severe disease (as described below). A second dose, however, may not be beneficial if there was little response to the first dose.

Glucocorticoids

Several scoring systems, including The Kobayashi, Egami and Sano scores, have been developed to identify children at highest risk of IVIG resistance and, hence, highest risk of developing CAA. A high risk patient is regarded as one where the risk of CAA is 20-30% despite IVIG treatment, and in Japan is identified as those patients with a Kobayashi score ≥5. The Kobayashi criteria, however, were found to be non-reliable in non-Asian populations. Glucocorticoids (GC) have been used for decades to treat similar inflammatory conditions and are increasingly used as primary treatment for severe KD. The Japanese RAISE trial, and several meta-analyses provide high level evidence for using GC as primary adjunctive treatment for patients with severe (high-risk) KD. Results of using GC as rescue treatment are less encouraging, suggesting that early use of GC is crucial to impact CAA outcomes.

The addition of GC to IVIG is currently recommended in Europe for primary treatment only for severe KD cases defined pragmatically; or for rescue treatment. GC should be added for those with:

1. IVIG failure: ongoing fever, and/or persistent inflammation or clinical signs ≥48 h after receiving IVIG
2. Severe disease: persistently elevated CRP, liver dysfunction, hypoalbuminaemia, anaemia, haemophagocytic lymphohistiocytosis, or shock.
3. Patients who already have evolving coronary and/or peripheral aneurysms with ongoing inflammation at presentation.

Two suggested GC regimens that can be used are: methylprednisolone 0.8 mg/kg IV for 5-7 days OR until CRP normalizes; then convert to prednisolone 2 mg/kg/day PO and wean off over the next 2-3 weeks; or methylprednisolone 10-30 mg/kg IV once a day for 3 days, followed by prednisolone 2mg/kg/day PO until day 7 OR CRP normalizes; then wean over the next 2-3 weeks (4). There are no data to support the use of one regimen in preference over the other.

Glucocorticoids for all KD patients?

The KD-CAAP Trial

We are currently exploring the hypothesis that GC used as adjunctive treatment may reduce the frequency of refractory KD and thus may improve coronary outcomes in the Kawasaki disease coronary artery aneurysm prevention (KD-CAAP) trial (ISRCTN71987471). Given the aforementioned high CAA complication rates seen in the UK and across Europe (16-42%), all KD patients are arguably at high-risk of CAA despite IVIG and could therefore potentially benefit from adjunctive GC as primary treatment. KD-CAAP will determine the efficacy and safety of adjunctive prednisolone 2mg/kg/day combined with IVIG/aspirin for prevention of CAA in unselected KD patients across Europe, compared with IVIG/ aspirin alone. The primary outcome is CAA frequency within 12 weeks. Until the results are known, we recommend following the SHARE guidelines regarding GC use for KD (4).

Anti-TNF (infliximab)

Animal data suggest a role for anti-tumour necrosis factor (TNF)-α therapy for the treatment of KD. In addition, serum TNF-α has been shown to be elevated in KD patients, and higher levels correlate with the development of CAA. While antagonism of TNF with infliximab, a chimeric anti-TNF monoclonal antibody, was found to be safe and well-tolerated in retrospective studies by Burns et al, phase III randomized controlled clinical trials using infliximab failed to demonstrate superiority to IVIG alone on coronary aneurysms. More recently, the KIDCARE trial, which aimed to compare infliximab with second IVIG, showed no significant difference between the groups in respect to laboratory markers of inflammation and coronary artery disease.

IL-1 blockade (anakinra)

There has been abundant evidence from human patients, genetic studies, and experimental mouse models that support the involvement of interleukin-1β (IL-1β) in the pathogenesis of KD. Anakinra is a competitive inhibitor to both IL-1α and IL-1β and acts by blocking the IL-1 binding to the IL-1 receptor. The Kawakinra study, a phase 2 clinical trial, aimed to determine the efficacy, safety and tolerability of blocking IL-1 signalling in patients with acute KD who are unresponsive to treatment with IVIG. While this study supported the early use of anakinra in cases refractory to IVIG, the effect on the KD symptoms and inflammation parameters took an average of 14 days to achieve. Ultimately, the study lays down the groundwork for controlled clinical trials to fully further evaluate the efficacy of anakinra as a first line treatment for KD.

Ciclosporin

Several studies have shown that T cell signalling pathway genes are associated with KD susceptibility, IVIG resistance, and increased risk of CAA in Asian and US children. This suggests that calcineurin inhibitors, such as ciclosporin, may be plausible for the treatment of KD. A recently reported RCT of 175 high risk Japanese KD patients randomised to receive IVIG versus IVIG plus ciclosporin (5 mg/kg per day for 5 days) found that incidence of coronary artery abnormalities was lower in the ciclosporin treatment group (12 [14%] of 86 patients vs 27 [31%] of 87 patients; risk ratio 0·46; 95% CI 0·25–0·86; p=0·010). No difference was found in the incidence of adverse events between the groups (9% vs 7%; p=0·78). Thus, combined primary therapy with IVIG and ciclosporin was safe and effective for favourable coronary artery outcomes in Kawasaki disease patients who were predicted to be unresponsive to IVIG. Ciclosporin therefore may also have a role for refractory KD although there are a few data that specifically address that question.

Conclusion

We provide a summary (Figure 1) of how we approach the treatment of refractory KD. We emphasize that the purpose of this approach is to rapidly switch off systemic inflammation with the intention of preventing CAA. We suggest that the therapeutic target of “zero fever, zero CRP” serves well as an aide memoir to assess the efficacy of such an approach and moves us away from the over-reliance on resolution of fever as the sole metric of success for inflammation amelioration, which in our opinion may have contributed to the recently described high CAA rates in the UK (19%), USA (13%), Skane, Sweden (16%), Germany (43%) and Moscow, Russia (30%) despite IVIG treatment.

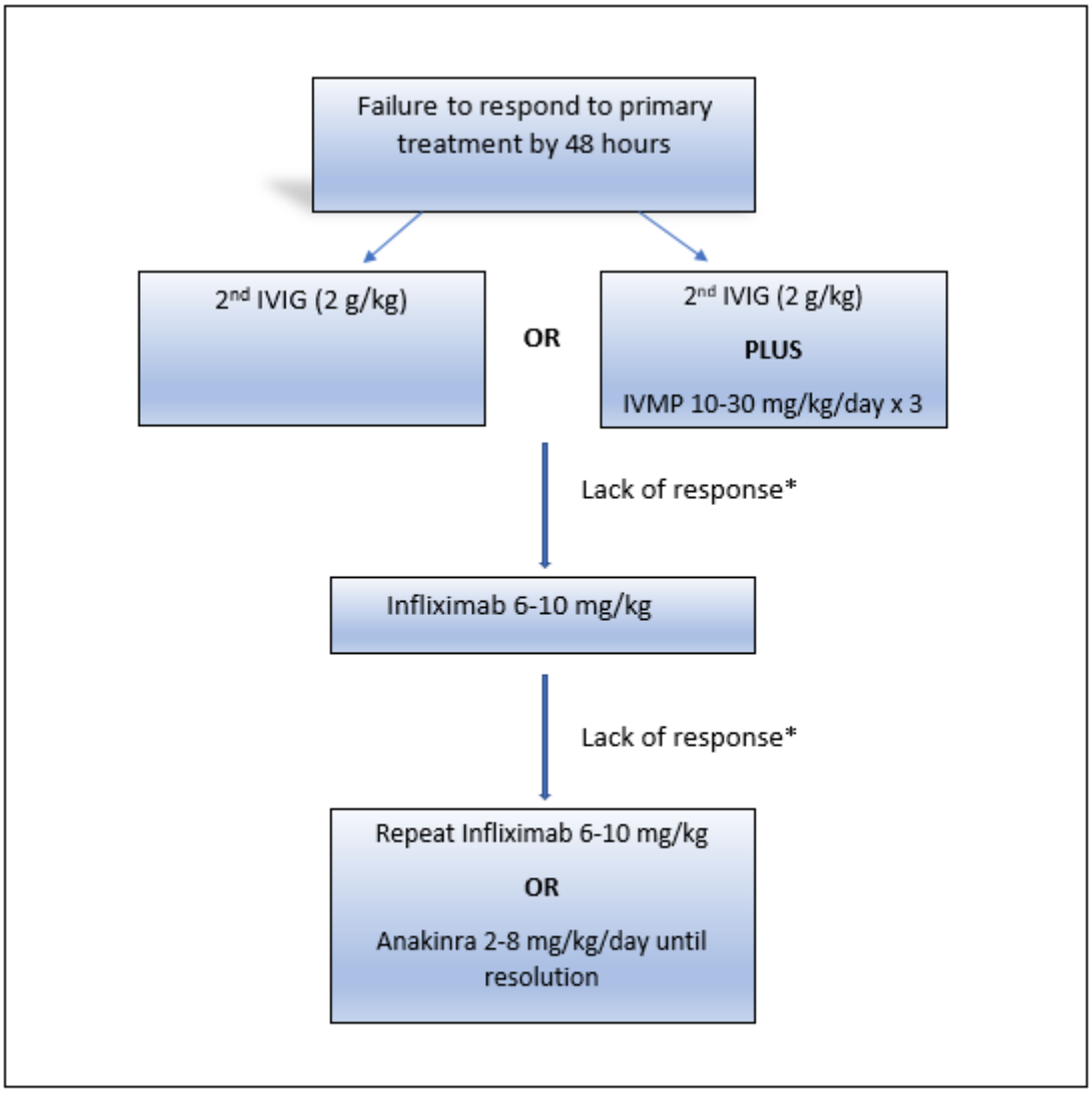

Figure 1 – Refractory Kawasaki Disease

IVIG=Intravenous immunoglobulin

IVMP=intravenous methylprednisolone

*Failure to achieve resolution of fever and rapid fall in CRP (should halve every 24 hours)

Practice Points

- Kawasaki disease is a medium vessel vasculitis typically affecting children under the age of 5 years, with predilection for causing CAA.
- Early recognition and treatment of KD with intravenous immunoglobulin (IVIG) has been shown to reduce the occurrence of CAA.
- Recently, high CAA rates have been observed seen in the UK and across Europe despite IVIG
- The addition of glucocorticoids (GC) to IVIG is currently recommended in Europe only for high risk cases. The KD-CAAP trial is currently exploring the efficacy of GC for unselected cases for the prevention of CAA.
- Treatment of refractory KD aims to rapidly switch of systemic inflammation (aim for “zero fever, zero CRP”) with the intention of preventing or limiting coronary injury.
- Beyond IVIG and GC, treatment of refractory KD may include anti-TNF, IL-1 blockade, or ciclosporin.

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Criterion	Description
Fever	Duration of 5 days or more, plus four of five of the following:
1. Conjunctivitis	Bilateral, bulbar, conjunctival injection without exudate
2. Lymphadenopathy	Cervical, often >1.5 cm usually unilateral
3. Rash	Maculopapular, diffuse erythroderma or erythema multiforme
4. Changes of lips or oral mucosa	Red cracked lips, strawberry tongue or diffuse erythema of oropharynx
5. Changes to extremities	Erythema and oedema of palms and soles in acute phase and periungal desquamation in subacute phase

Table 1 - American Heart Association Diagnosis of Kawasaki Disease 2017