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Predictors and management of intravenous immunoglobulin-resistant Kawasaki disease

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Kawasaki disease (KD) is a systemic vasculitis that mainly affects younger children. Intravenous immunoglobulin (IVIG) resistant cases are at increasing risk for coronary artery complications. The strategy on prediction of potential nonresponders and treatment of IVIG-resistant patients is now controversial. In this review the definition and predictors of IVIG-resistant KD and current evidence to guide management are discussed.

Key words: Kawasaki disease, Intravenous immunoglobulin, Resistance, Predictors, Management

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Introduction

Kawasaki disease (KD) is an acute febrile pediatric illness, a vasculitis of unknown etiology,[1] and is the most common cause of acquired cardiac disorders in pediatric patients. Up to 20% of patients with KD who remain febrile after administration of first dose of intravenous immunoglobulin (IVIG) plus aspirin are classified as having IVIG-resistant disease.[2] Studies have found nonresponders to initial IVIG therapy to have a higher risk for coronary artery lesion (CAL), including aneurysms, compared with responders.[3-5] Analysis in 362 patients with KD from 1998 to 2006 revealed that aneurysms developed in 9 of 60 (15%) IVIG-resistant patients as compared with 9 of 302 (3%) IVIG-responsive patients (P=0.0008). IVIG resistance was strongly associated with an increased coronary artery aneurysm rate.[5]

Recent studies have investigated factors for predicting resistance to IVIG and CAL in patients with KD, but the results have been conflicting.

Many experts recommend retreatment with a second dose of IVIG for IVIG-resistant KD.[2] Patients who fail to respond to 2 doses of IVIG present a unique challenge because there is no clear guidance for an appropriate treatment regimen in this small group of refractory KD patients who remain febrile. Guidelines from the American Heart Association (AHA) recommend a second dose of IVIG, methylprednisolone, a longer tapering course of prednisolone or prednisone plus IVIG, or infliximab for patients resistant to IVIG.[2]

Definition of IVIG resistance

The AHA defines IVIG-resistant KD as "recrudescent or persistent fever at least 36 hours following completion of the first dose of IVIG."[2] But some studies used 24 hours or 48 hours instead of 36 hours. Some use the term "refractory" instead of "IVIG-resistant" KD.

Some of the patients who have persistent or recurrent fever more than 24 hours after completion of the initial treatment should also be assessed for concomitant infection[6] or rare hemophagocytic lymphohistiocytosis.[7] Children with KD and concomitant infection are more

likely to have persistent fever after treatment and this association increases the likelihood of receiving a second dose of IVIG but not the risk of coronary complication. Accordingly, prospective studies to distinguish true IVIG resistance from infection-induced persistent fever is warranted.

Predictors of IVIG resistance

Persistent or recurrent fever after IVIG treatment is one of the strongest risk factors for the development of coronary artery aneurysm. Many retrospective studies have identified potential risk factors that predict which patients will require further therapy for refractory disease. In Japan, risk score systems are used to predict patients at high risk of IVIG resistance[8,9] and initial therapy is intensified in those patients. Kobayashi et al.[8] constructed a scoring model and suggested: 2 points for days of illness at initial treatment ≤4, 2 points for sodium <133 mmol/L, 2 points for aspartate aminotransferase (AST) ≥100 IU/L, 2 points for % Neutrophils ≥80, 1 point for age ≤12 months, 1 point for C-reactive protein (CRP) ≥10 mg/dL, 1 point for platelets ≤300,000/mm^3, low risk: 0–3; high risk: 4–6, very high risk >7. Egami et al.[9] constructed a scoring model and suggested: 2 points for AST >80 IU/L, 1 point for age ≤6 months, 1 point for days of illness at initial treatment ≤4, 1 point for platelets ≤300,000/mm^3, 1 point for CRP ≥8 mg/dL, low risk: 0–3; high risk >4. However, those risk scores did not prove useful in other ethnic populations,[10,11] and no single marker has been proven to predict resistance to treatment. The scoring systems have been constructed to identify patients likely to be resistant to IVIG and who may benefit from more aggressive initial therapy. Many studies aimed at evaluating the use of Japanese scoring systems failed to demonstrate real effectiveness and found them insufficiently accurate to be clinically useful in predicting IVIG resistance and coronary involvement in non-Japanese populations.

A meta-analysis comprising 2,745 IVIG-resistant KD patients conducted in 2016 by Baek and Song [12] revealed that higher total bilirubin, polymorphonuclear neutrophil (PMN), brain natriuretic protein (BNP), AST, alanine aminotransferase (ALT), and CRP levels, and lower sodium and albumin levels are predictive of IVIG-resistant KD, but white blood cell count, platelet count, and erythrocyte sedimentation ratio (ESR) had no effect as predictors of IVIG-resistant KD. Another meta-analysis comprising 4,442 IVIG-resistant KD patients conducted in 2018 by Li et al.[13] also showed the same results for higher total bilirubin, PMN, pro-BNP, AST, ALT, and CRP levels, and lower sodium and albumin levels. Additionally, the ESR in the IVIG-resistant group was also significantly higher

Table 1. Predictors of IVIG resistance in KD patients

Study	Study type	Nation	Year	Patients with IVIG resistance (n)	Risk factors
Kobayashi et al.[8]	Retrospective	Japan	2006	148	Days of illness at initial treatment ≤4, age ≤12 mo, AST ≥100 IU/L, CRP ≥10 mg/dL, PLT ≤300×109/L, Na ≤133 mmol/L, %N≥80%
Egami et al.[9]	Retrospective	Japan	2006	41	Age ≤6 mo, CRP ≥8 mg/dL, ALT ≥80 IU/L, PLT<300×10^9/L
Baek and Song[12]	Meta-analysis	Multinational	2016	2,745	Increased: Total bilirubin, PMN, BNP, AST, ALT, CRP Decreased: Na, albumin
Li et al.[13]	Meta-analysis	Multinational	2018	4,442	Initial administration of IVIG≤4.0 days after the onset of symptoms Increased: Total bilirubin, PMN, pro-BNP, AST, ALT, CRP, ESR Decreased: Na, albumin, PLT, Hemoglobin

IVIG, intravenous immunoglobulin; KD, Kawasaki disease; CRP, C-reactive protein; PLT, platelet; Na, sodium; N, neutrophils; PMN, polymorphonuclear neutrophil; BNP, brain natriuretic protein; AST, aspartate aminotransferase; ALT, alanine transaminase; ESR, erythrocyte sedimentation ratio.

Table 2. Treatment regimens for IVIG-resistant KD

Treatment agent	Description	Dose
IVIG[23]	IVIG	2-g/kg intravenous infusion for 12 hr
IVIG plus prednisolone[29,30]	IVIG plus steroid	2 g/kg IVIG plus intravenous prednisolone 2 mg/kg/day in 3 divided doses for 5 days until defervescence and CRP normalization, followed by the oral with tapering over 15 days
Infliximab[31-36]	Monoclonal antibody against TNF	5-mg/kg intravenous infusion for 2 hr
Etanercept[37]	Soluble form of TNF-α receptor	Three doses of etanercept (0.8 mg/kg/dose) subcutaneously. The first dose within 24 hr of completing IVIG which was defined as day 0. Subsequent doses administered at day 7 and day 14
Cyclosporine[38,39]	Calcineurin inhibitor	Start with intravenous 3mg/kg/day divided every 12 hr Switch to oral once afebrile >24 hr Oral: 8–10 mg/kg/day divided every 12 hr
Methotrexate[40]	Folic acid antagonist	10 mg/body surface area orally once a week until the fever subsids
Anakinra[41,42]	Recombinant IL-1β receptor antagonist	2–6 mg/kg/day by subcutaneous injection
Plasma exchange[43]	Replace plasma with albumin	Not applicable

IVIG, intravenous immunoglobulin; KD, Kawasaki disease; CRP, C-reactive protein, TNF, tumor necrosis alpha; IL, interleukin.

than that in the IVIG-sensitive group, and platelet count and hemoglobin levels were significantly lower in the IVIG-resistant group. The results differed by ethnicity. The risk factors for IVIG-resistant KD were also the initial administration of IVIG ≤4.0 days after the onset of symptoms. *N*-terminal probrain natriuretic peptide (NT-proBNP) has been shown in some, but not all, studies to predict or accompany resistance to IVIG treatment.[14-16]

Predictors of IVIG resistance in KD patients are summarized in Table 1. Many studies have shown that patients who are resistant to initial IVIG are at increased risk of developing coronary artery abnormalities. So, these patients should be retreated for presumed IVIG-resistant KD, unless there is clear evidence of another explanation for fever. Therefore, it is important to determine the effectiveness of IVIG soon after therapy, especially in resistant cases, to recognize a need for additional therapy. There is no mention in AHA 2017 guidelines, but several studies showed that, in KD patients who remain febrile despite IVIG treatment, the need for more aggressive therapy in IVIG-resistant cases can be recognized and additional therapy can be facilitated by laboratory parameters.[17,18] The patients who failed to defervesce after IVIG therapy were characterized by significantly higher values of post-IVIG white blood cell (WBC), % neutrophils, CRP, and NT-proBNP, compared with IVIG-responsive patients.[17] Another study reported that sustained higher WBC and CRP and lower total protein values were observed in the IVIG nonresponsive group at 24 hours after IVIG-termination, whereas the IVIG responsive group showed an approximately 40%–60% reduction of WBC and CRP values.[18]

These combinations of above variables can be useful to predict the need for further advanced therapy to prevent disease progression. Moreover, the author hopes to construct a more reliable risk scoring system for early detection of KD patients with IVIG unresponsiveness from the clinical and laboratory parameters.

In a recent study, the presence of any abnormalities at the initial echocardiogram may be associated with resistance to IVIG and development of CALs.[19] This result is similar with another study which state that coronary artery *z* score (baseline coronary dimensions adjusted for body surface area) at diagnosis was highly predictive of outcomes[20] and a baseline coronary artery *z* score ≥2.0 had a greater predictive utility for aneurysm development, which may be improved by early IVIG treatment and adjunctive therapies.[21]

In the future, by identifying and combining an additional genetic features, early and aggressive therapies may be used to reduce the risk of coronary complications.[22]

Treatment of IVIG-resistant KD

Many experts recommend retreatment with a second dose of IVIG for IVIG-resistant KD.[2] But there are no adequately powered prospective randomized trials to retreat IVIG in patients who fail initial IVIG treatment.[23] Patients who fail to respond to 2 doses of IVIG present a unique challenge because there is no clear guidance for an appropriate treatment regimen in this small group of refractory KD patients who remain febrile.

The use of corticosteroids in KD remains controversial. Corticosteroids for KD have been avoided since a retrospective study reported by Kato et al.[24] in 1979 in the pre-IVIG era. But others have reported the use of both IV methyprednisolone and oral corticosteroids with good results, predominantly in patients with refractory KD.[25] So administration of high-dose pulse steroids (with or without a subsequent course and taper of oral prednisone) may be considered as an alternative to a second infusion of IVIG. A recent study on the use of corticosteroids in KD has shown that the use of steroids in the acute phase of KD as either first-line or second-line treatment can be associated with improved coronary artery abnormalities with moderate-quality evidence.[26] But another recent study shows that IVIG-resistant patients with alternative corticosteroid therapy more frequently develop CAL than those without corticosteroid therapy.[27]

One meta-analysis concluded that steroids can protect against coronary artery abnormalities when used as early initial therapy (as opposed to rescue therapy), particularly in children at high risk for IVIG resistance.[28] The Randomized controlled trial to assess immunoglobulin plus steroid efficacy for Kawasaki disease (RAISE) study showed that additional prednisolone improved coronary artery outcomes in patients with KD at high risk of IVIG resistance.[29] A multicentre prospective cohort study in Japan also showed primary IVIG plus prednisolone therapy had an effect similar to that seen in the RAISE study in reducing the nonresponse rate and decreasing the incidence of coronary artery abnormalities.[30] A primary IVIG and prednisolone combination therapy might prevent coronary artery abnormalities and contribute to the lowering of medical costs.

In refractory KD patients, anti-tumor necrosis factor (TNF)-α agents, such as infliximab, have been investigated. Overall, it appears that infliximab causes rapid defervescence resulting in a shorter length of hospital stay, and is relatively well tolerated. Retrospective studies have reported response rates (defined by a reduction in fever and CRP level) of 81.3%–91.7% when infliximab was used as a second-line agent.[31-36] Most reports failed to detect beneficial effects in the prevention of coronary aneurysms. However in a trial involving children with KD, the addition of infliximab to primary IVIG treatment reduced fever duration, some markers of inflammation, and left anterior descending coronary artery *z* score.[35] And in our recent study, the early infliximab treatment group rather than the late treatment group had a reduced incidence of significant coronary artery aneurysm (*z* score >5) in patients with IVIG-resistant KD.[36]

A soluble form of TNF receptor fusion protein that antagonizes the effects of endogenous TNF (etanercept) showed satisfactory results in several cases of refractory KD leading to a decline in fever and inflammatory activity and to a regression of coronary abnormalities.[37]

A small, open, single-arm pilot trial in Japan studied cyclosporine (calcineurin inhibitors) treatment in 28 children who remained febrile after administration of 2 doses of IVIG. Overall, 78% of patients responded. Nine patients developed hyperkalemia, but none had serious adverse effects.[38,39]

The immunosuppressive agent methotrexate has been occasionally used to treat IVIG-resistant KD but did not affect the improvement or prevention of CAL.[40]

Anakinra, a recombinant, nonglycosylated form of the human interleukin (IL)-1 receptor antagonist, used late in the disease course led to a rapid and sustained improvement in clinical and biological inflammation. But analysis did not show either a striking or a rapid decrease of coronary dilatations.[41,42] One patient with rapid increase of coronary artery aneurysms died of massive pericardial hemorrhage probably due to aneurysm rupture.[42] Clinical trials are in progress to evaluate the efficacy of IL-1 blockade in children with acute KD.

The outcomes of plasma exchange for KD refractory to IVIG may be favorable,[43] particularly if it is initiated before CAL arises. But because of its risks, plasma exchange should be reserved for patients in whom all other kinds of medical therapies have failed. Treatment regimens for IVIG-resistant KD are summarized in Table 2.

Conclusions

Some patients with KD have persistent or recurrent fever despite treatment with IVIG and aspirin. Prolonged fever is a risk factor for coronary artery sequelae in KD. The author reviewed the literature relating to the predictors and current evidence to guide management of resistant KD.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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