ejpmr, 2024, 11(11), 423-432

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

TREATMENT APPROACHES FOR KAWASAKI DISEASE: A NARRATIVE REVIEW ON CURRENT PRACTICES

Edwin Dias[1,2*] and Yeshashwini Naik[3]

[1]HOD and Professor, Department of Paediatrics, Srinivas Institute of Medical Sciences and Research Centre, Mangalore, Karnataka State, India.

[2]Adjunct Professor, Srinivas University, Director of Research and Publication, India.

[3]Final Year Pharm D, Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka State, India.

***Corresponding Author: Edwin Dias**

HOD and Professor, Department of Paediatrics, Srinivas Institute of Medical Sciences and Research Centre, Mangalore, Karnataka State, India.

Article Received on 21/09/2024 **Article Revised on 11/10/2024** **Article Accepted on 31/10/2024**

ABSTRACT

Kawasaki disease (KD) is a medium vessel vasculitis that predominantly affects the coronary arteries and is recognized as the leading cause of acquired heart disease in children.[7] KD diagnosis is still a clinical challenge, and there is no confirmatory lab test available to diagnose it. The KD diagnostic criteria have undergone periodic revisions. The American Heart Association's and the Kawasaki Disease Research Committee's guidelines are the two sets of diagnostic criteria that have been applied to this ailment the most.[7] The clinical and epidemiologic aspects of KD strongly point to an infectious cause. KD is prevalent around the world, with Japan, Korea, and Taiwan having the highest rates because of heightened genetic vulnerability in Asian people.[6] Aneurysms can occur from delayed treatment, treatment refractory conditions or missing diagnoses, and in up to 25% of affected individuals, these events can result in severe cardiac sequelae, including myocardial infarctions. Thus, in developed countries, KD is the most commonly acquired cardiac disease.[5] The therapeutic approaches for patients with Kawasaki disease are summed up in this review. The goal of treatment is to reduce the risk of coronary artery aneurysm formation by reducing coronary artery inflammation with intravenous immunoglobulin (IVIG), aspirin, corticosteroids; additionally, anticoagulant, antiplatelet, and thrombolytic agents are used to treat cardiovascular complications of the disease. Supplementary to the primary treatment plan, supportive care is also necessary.[10]

KEYWORDS: Kawasaki disease, Coronary artery aneurysm, Intravenous immunoglobulin.

INTRODUCTION

Kawasaki disease is a systemic vasculitis that affects mostly the walls of medium-sized arteries.[5] It is an acute, self-limiting febrile disease that primarily affects children under five years old and has no known etiology. Fever, affection of the mucous and skin membranes, conjunctivitis, and cervical lymphadenopathy are the primary symptoms.[5] It is known to be the primary cause of acquired heart disease in young people.[7]

The first account of Kawasaki disease was published in a 1967 paper by Japanese pediatrician Tomisaku Kawasaki, who provided a thorough account of 50 children who had this type of vasculitis. In 1970, subsequent documentation of the cardiac sequelae was observed, which resulted from an investigation into 10 post-mortem cases of abrupt cardiac death after KD diagnosis.[5, 8]

The diagnostic criteria for KD have undergone periodic revisions. The most frequently used diagnostic criteria for this condition are as follows:

1. Kawasaki Disease Research Committee guidelines (Japanese guidelines), 2002.
2. American Heart Association (AHA) guidelines, 2004.

These criteria have their basis in clinical observations and bear little resemblance to the initial case reports of KD provided by Dr. Kawasaki.[30] The key difference between the AHA and Japanese criteria is that the former do not require a fever lasting more than five days, whereas the japanese criteria must.[7] The American Heart Association's (AHA) diagnostic guidelines for KD are the most commonly used criteria worldwide.[3]

Undiagnosed and untreated Kawasaki disease increases the risk of cardiovascular problems, including coronary artery aneurysms (CAA), Other systemic KD complications are represented by anemia, electrolyte imbalance (especially hyponatremia), paralytic ileus, hypoalbuminemia, liver dysfunction, cholecystitis, seizures, vomiting, dehydration, diarrhea and heart failure,[4] Pericarditis with pericardial effusion, valvulitis and rupture of the coronary arteries leading to

hemopericardium and sudden death.[10] There have also been reports of macrophage activation syndrome (MAS) in KD cases.[4] Acute phase cardiac issues will affect roughly 9% of individuals, whereas cardiac sequelae will affect about 3% of patients.[10]

The objectives of KD treatment are reducing fever, edema, preventing heart damage, preventing blood clots, and preventing or reducing damage to the arteries. Reducing inflammation (and subsequent arterial damage) and minimizing potentially fatal thrombosis linked to abnormalities in the coronary arteries are the main objectives of the early treatment of acute KD. Currently, high-dose intravenous immune globulin combined with aspirin is the cornerstone of treatment.[9]

EPIDEMIOLOGY

The prevalence of KD differs by ethnicity and geography:

The frequency of KD is 4–25 incidents per 100,000 children under the age of five in North America, Europe, and Australia. The incidence peaks in children between the ages of 18 and 24 months in the US. Northeast Asia: Compared to North America and Europe, the incidence of KD is 10–30 times higher there.

The incidence rate in Japan is 265 cases per 100,000 children under the age of.[5] In India and China, rapid economic expansion and industrialization are probably the reason for the rising incidence of KD in these countries.[10, 11, 12]

ETIOLOGY

Since its discovery in 1967, a potential agent has not been found despite years of research. The presence of an agent or infection that is etiologically associated to KD is strongly suggested by epidemiological features.[9,31]

.

The etiology of KD, toxic shock syndrome, and scarlet fever are similar, leading to the suggestion that they are caused by bacterial toxins or superantigens. Nevertheless, no bacterial toxin has been found in KD patients' peripheral blood.[9]

The lung antigen confined to intracytoplasmic inclusion bodies, which were recognized by RNA and protein staining.[6, 19]

Different populations may have different genetic susceptibilities, which could account for the higher rates in Asian populations. Exogenous factors that contribute to illness expression in genetically susceptible individuals are suggested by seasonal and geographical patterns as well as observed relationships with wind directions.[5] Furthermore, a Viral etiology is strongly suggested by the high expression of cytotoxic T cell and interferon pathway genes in the coronary arteries of children who have died of KD, as well as the presence of CD8T cells in the inflammatory infiltrate.[6]

PATHOGENESIS

1. **Acute infection**
   Infection of the ciliated bronchial epithelium by the KD ubiquitous agent typically results in asymptomatic infection and KD in a small percentage of children who are genetically susceptible. Epidemics of KD can be explained by an as-yet-unidentified respiratory agent, which can occasionally cause outbreaks of sickness or rare cases. In previously infected individuals, it may continue to be persistent as cytoplasmic inclusion bodies with occasional shedding.
2. **Blood stream spread and immune response**
   The KD agent enters the bloodstream through macrophages and targets the coronary arteries and other locations. Antigen-specific IgA plasma cells and other cells then mount an adaptive immune response, but coronary arteries may sustain damage.
3. **After infection**
   After recovery, the KD patient is nearly always immune, which explains why 97–99% of KD children do not recur and why the majority of them do not experience other health issues.
4. **Spread through population**
   The KD agent can be transmitted from a close contact who has been infected in the past and intermittently sheds the agent (other seasons) or from a community contact who has a primary acute infection (particularly in the winter and spring).[6]

DIAGNOSIS

KD can be diagnosed using clinical criterias. Since the distinctive clinical symptoms might not be visible at the moment, a comprehensive history and physical examination are crucial. The presence of at least five days of fever and at least four out of five clinical characteristics are prerequisites for the traditional clinical criteria for diagnosing KD.[9]

Kawasaki Disease Research Committee lists the following as the main symptoms (at least five of them):
fever lasting longer than 5 days. bilateral conjunctivitis, rash on the skin, alterations in the oral mucosa (strawberry tongue, fissured lips, diffuse injection), Peripheral extremity changes (first stage: palm and sole edema and redness; recovery stage: fingertip peeling), cervical lymphadenopathy that is acute, non-purulent, and more than 1.5 cm in diameter.

If a coronary aneurysm or dilatation is found by 2D echocardiography or coronary angiography, patients with four of the main symptoms can be diagnosed with KD. According to the Japanese criteria, KD can be diagnosed as early as the first, second, third, or fourth day of a fever, even if the symptoms do not align with the AHA guidelines.

According to the 2017 update of the American Heart Association's diagnostic guidelines for KD, the condition can still be diagnosed in patients who have a fever that

lasts longer than four days and who also exhibit at least four of the five main clinical symptoms, particularly if they have either palmar or plantar erythema or edema of the hands and feet (4 limb changes) and it is called 4-4-4 rule.[3,33]

American Heart Association Guidelines:
At least five days of fever and at least four of the five conditions listed below: Lip cracking and erythema, infection of bilateral bulbar conjunctivas without exudate, in acute phase Hand and foot edema, periungual desquamation in the subacute phase, or maculopapular rash, widespread erythroderma, or erythema multiforme-like rash Usually unilateral, strawberry tongue, erythema of the oral and pharyngeal mucosa, and cervical lymphadenopathy (1.5 cm indiameter).

Meet each of the four requirements listed below: fever lasting five days or more, ESR of 40 mm/h or CRP of 3.0 mg/dL are at least two of the primary clinical signs of KD. Three or more of the six additional laboratory requirements listed below: albumin 3.0 g/dL, anaemia for age, a platelet count of 450,000/mm3 following the seventh day of fever, elevated alanine transaminase, white blood cell count of 15,000/mm3, urine white blood cells 10/hpf.[3,32]

DIAGNOSIS OF INCOMPLETE KAWASAKI DISEASE

Young children with unexplained fever and patients who do not fully meet the traditional clinical criteria might also be diagnosed with incomplete KD. According to the 2017 AHA guidelines. Incomplete KD should be evaluated in infants who have had an unexplained fever for at least seven days and in children who have had a fever for at least five days while exhibiting two to three clinical signs of KD.

Three additional laboratory criteria and non-specific laboratory results of elevated inflammatory markers (CRP and ESR) are regarded as reliable evaluations for incomplete KD.

Treatment must be initiated if the laboratory and echo results show incomplete Kawasaki disease, if CRP ≥3.0 mg/dL and/or ESR ≥40 mm/h.

3 or more Laboratory Findings:
Albumin≤3.0 g/dL, Anemia for age, Plt count ≥450,000 after 7th day of fever, Elevated ALT, Urine WBC ≥10/hpf, WBC≥15,000/mm3.

Positive ECHO, is considered in dignosing incomplete KD.[9]

DIFFRENTIAL DIAGNOSIS

Kawasaki disease is frequently mimicked by a number of infections, including Adenovirus and KD both manifest as conjunctival injection; the key distinction is that adenovirus produces conjunctival exudates, whereas KD does not. By looking at whether the lymphadenopathy is unilateral or bilateral, one can distinguish KD from lymphadenitis; in more than half of patients, Kawasaki usually manifests unilaterally.

Retropharyngeal edema, which may indicate a potential retropharyngeal abscess, can be caused by KD. But unlike KD, real RPA will have unusual imaging and clinical symptoms. KD involves the eyes and joints, whereas toxic shock syndrome and scarlet fever do not.

The symptoms of Kawasaki disease also resemble those of other immunologic reactions, including infantile polyarteritis nodosa, systemic lupus erythematosus, juvenile idiopathic arthritis, and various drug hypersensitivity reactions. These can be distinguished from KD based on the number of affected joints, chronicity, and the lack of typical clinical criteria.[10,27,28]

TREATMENT

PRIMARY TREATMENT REGIMEN

Reducing inflammation (and consequently arterial damage) and averting potentially lethal thrombosis associated with coronary artery abnormalities are the primary goals of KD treatment. Aspirin (ASA) and high-dose intravenous immune globulin (IVIG) are currently the mainstaysoftreatment.[9]

1. Intravenous immune globulin (IVig):

Plasma from several blood donors is used to create this biological product.

MOA: IVIG appears to have a broad anti-inflammatory impact. alteration in the production of cytokines, elevated activity of regulatory T-cells, suppression of antibody formation, neutralisation of poisons or other harmful chemicals, and development of anti-idiotypic antibodies.[2] Consequently, by stopping the evolution of KD, coronary artery aneurysms are inhibited.[23]

DOSING: As a first line of treatment, ASA and a single IVIG infusion at a rate of 2 mg/kg over 10–12 hours should be administered. Children with KD should still receive treatment after the tenth day of sickness if there are ongoing symptoms of inflammation, even though IVIG should ideally be given during the first ten days of illness.[24,25]

Aseptic meningitis, Coombs-positive haemolytic anaemia, and generalised infusion reactions are among the adverse reactions that patients should be particularly watched for during infusion.

After high-dose IVIG, live vaccinations, especially those for varicella, mumps, and measles, should be postponed for 11 months.[4,9]

Keep an eye on your vital signs, fluid intake and output, and responses connected to infusion. Haemolytic

transfusion reaction: track igG levels to evaluate treatment efficacy.

SIDE EFFECTS: fever, headache, hemolytic reactions and dyspnea.

1. Aspirin (acetylsalicylic acid/ASA)

ASA has important antiplatelet activity (at low doses) and anti-inflammatory activity (at high doses)

MOA: It inhibits the cyclooxygenase (COX) enzyme from producing prostaglandins (PGs), which are in turn in charge of fever, swelling, inflammation, and discomfort. Consequently, an anti-inflammatory action is produced, reducing its production hinders platelet aggregation since it also inhibits COX 2 in platelets, which lowers the synthesis of thromboxane A2, which is necessary for platelet aggregation and activation.

DOSING: ASA is given every 6 hours during the acute phase of sickness, with a daily dose of 80–100 mg/kg/d 10 in the US and 30–50 mg/kg/d in Japan and Western Europe. There is no evidence to support the superiority of either ASA dosage.

Until the fourteenth day of the sickness and for at least 48 to 72 hours following the end of feverLow-dose ASA (3 to 5 mg/kg/d) is started and sustained after high-dose ASA is stopped until the patient shows no signs of coronary abnormalities 6 to 8 weeks after the sickness started.

Although there is no proof that moderate-dose (30–50 mg/kg/d) to high-dose (80–100 mg/kg/d) ASA decreases coronary artery aneurysms, it is reasonable to administer it until the patient is afebrile.[9]

ECG should be monitored during acute illness and at follow-up to determine the involvement of the coronary arteries.

SIDE EFFECTS: tarry, black stools, unusual bleeding, severe or persistent stomach discomfort, weakness, and blood particles that resemble coffee grounds being vomited.

Because it counteracts the antiplatelet activity of ASA, ibuprofen is contraindicated.[1, 22]

In patients who present with influenza or varicella and KD, Alternative antiplatelet agent should replace ASA for a minimum of 2 weeks.[9]

ADJUNCTIVE THERAPY

1. Corticosteroids

Several studies were conducted in different countries showed that the children treated with ASA (30 mg/kg/d) and IVIG (1 g/kg for 2 consecutive days) plus intravenous prednisolone or methyl prednisolone.

A) Methylprednisolone

MOA: Methylprednisolone inhibits the advancement of coronary artery involvement by decreasing the function of lymphocytes and other immune response cells, reducing the migration of polymorphonuclear leukocytes, and reversing enhanced capillary permeability.

DOSING: The steroid group saw a quicker drop in CRP levels, a shorter duration of fever, and a reduced incidence of coronary artery anomalies and retreatment after receiving a single infusion (30 mg/kg/d) followed by an oral taper. One As of right now, the American Heart Association suggests that high-risk patients with acute KD who can be identified before treatment begins should be treated with a longer course of corticosteroids (such as tapering over two to three weeks), IVIG 2 g/kg, and ASA.[1, 9]

Multiple Japanese clinical studies support the use of corticosteroids as adjunctive therapy for children at high risk for IVIG resistance.[9]

A close monitoring of vital signs, ECG, and blood pressure is required during pulse.[4, 21]

SIDE EFFECTS: Hyperglycemia, Bradycardia, hypertension and hypothermia.

B) Prednisolone

MOA: By inhibiting polymorphonuclear leukocyte movement, reversing enhanced capillary permeability, and suppressing the extracellular release of HMGB-1 and related inflammatory pathways, prednisolone lowers inflammation.

DOSING: Prednisone can be taken orally after fever and improvement of inflammatory indicators. If used in conjunction with IVIG as a first-line treatment, the dose is 2 mg/kg/day given intravenously in three doses. Prednisone can be continued for five days once CRP returns to normal. once that, it is lowered to 1 mg/kg/day in two doses for an additional five days, and then to 0.5 mg/kg/day for an additional five days. 3

SIDE EFFECTS: diabetes, glaucoma, chorioretinopathy, cataracts, pancreatitis, arrhythmia, congestive heart failure, liver failure, shock, infection, gastrointestinal bleeding or perforation, and Legg-Calvé-Perthes disease.[4]

2. Infliximab

MOA: A chimeric monoclonal antibody called infliximab blocks TNF-α to reduce inflammation. Coronary artery lesions (CALs) are associated with higher levels of TNF-alpha, a pro-inflammatory cytokine, in KD patients.

DOSAGE: IV infusion of 5 mg/kg administered over two hours.

For the initial treatment of acute KD, infliximab adjunct therapy is not yet recommended.[9]

Fever duration and the rate of inflammatory marker normalisation were reduced when infliximab was added to IVIG for initial treatment; however, neither the rate of CAA nor the rate of IVIG resistance were lowered.[9,20]

Infliximab successfully lowered levels of proinflammatory cytokines, indicating a reduction in systemic inflammation. However, markers associated with vasculitis, like vascular endothelial growth factor and S100 proteins, remained high, suggesting that while systemic inflammation was addressed, the vasculitis itself was not fully suppressed. Adding infliximab to the initial IVIG therapy is safe but does not stop the recurrence of fever.[1]

SIDE EFFECTS: Potential side effects of infliximab include infusion reactions such as itching, anaphylaxis, skin rashes, headaches, angioedema, and bronchospasm. Symptoms of hypersensitivity can develop up to three days after the infusion and may include muscle pain, among others.[4]

3. Etanercept

MOA: A soluble TNF receptor called etanercept attaches itself to TNF-beta and TNF-alpha to stop them from starting inflammatory processes.

The study on IVIG and etanercept treatment for escalation of initial therapy was published.

DOSAGE: Three weekly subcutaneous injections of 0.8 mg/kg of etanercept.[40]

Etanercept did not significantly lower IVIG resistance; however, it did reduce the progression of coronary artery dilatation in individuals with baseline abnormalities and improve IVIG resistance in patients older than one year ($p = 0.03$). The American Heart Association does not currently advise using etanercept as an adjuvant treatment.[9]

SIDE EFFECTS: Bleeding, headaches, respiratory infections, diarrhoea, and pale skin.

IVIG RESISTANT KAWASAKI DISEASE

Failure to respond to early IVIG therapy is a sign of a resistant KD. After 36 hours following the cessation of IVIG infusion, patients may experience a persistent or recurrent fever (> 38 °C, axillary or rectal). Over 10% of KD patients experience this incident. The higher frequency of CAA in this patient subgroup is thought to be explained by IVIG non-responsiveness, which may be a reflection of the degree of the underlying inflammation.[1]

Refractory KD is often treated with infliximab, retreatment with IVIG + prednisone, or a repeat IVIGinfusion.[9]

Retreatment of IVIG IVIG should be given again to patients with refractory KD at the same dosage (2 mg/kg as a single infusion). Series of retrospectives have indicated effectiveness in this approach.[9]

1. Corticosteroids

The best steroid treatment for refractory KD is still up for debate. In lieu of a second IVIG infusion, high-dose pulse steroids (IVMP 20–30 mg/kg IV for 3 days with or without PO prednisolone taper) may be used to treat patients who have recurrent fever following further IVIG infusions. Another suitable regimen is to administer a lengthier course of prednisolone (2 mg/kg/day IV split every 8 hours until afebrile, then PO prednisolone until CRP normalised, followed by a 2- to 3-week taper) with IVIG and ASA.[10]

2. Infliximab

Single infusion: 5 mg/kg IV given over 2h.

It may be considered to be an alternative to a corticosteroids or 2nd infusion of IVIG for refractor KD.

3. Cyclosporine

MOA: The calcineurin inhibitor cyclosporin inhibits the Ca2+/NFAT signalling pathway, which is linked to immunological hyper-reactivity and has been linked to the development of CAA and KD vulnerability.[9]

DOSING: IV: 3 mg/kg/day, split every 12 hours PO: split every 12 hours, 4–8 mg/kg/d If the second IVIG infusion, infliximab, or corticosteroids have not worked for a patient with refractory KD, the dose may be adjusted to reach a 2-hour peak level of 300–600 ng/mL. After two weeks of treatment or until the patient is afebrile and showing clinical improvement with a CRP of less than 12 mg/dL, cyclosporin should be continued. After then, the dosage should be reduced by 10% every three days until it reaches 1 mg/kg/day. [1,9]

SIDE EFFECTS: hirsutism, hypertension, hypomagnesaemia, and hypercalcemia.[4]

4. Anakinra

An IL-1 receptor antagonist called anakinra has been used to treat extremely refractory KD.

MOA: It is an antagonist of the recombinant interleukin-1 (IL-1) receptor with immunomodulatory and anti-inflammatory properties.

DOSING: subcutaneous injection of 2–6 mg/kg/day.[1,9]

SIDE EFFECTS: They may affect the respiratory system (sinusitis, influenza-like disease, upper respiratory infections, and infrequently pneumonia), the

gastrointestinal tract (nausea, abdominal discomfort, diarrhoea, and hyper-transaminasemia), or the skin (bruising, local infections, and urticarial-like lesions).

OTHER TREATMENT MODALITIES

Cytotoxic agents and Plasma exchange such as cyclophosphamide have been used in particularly refractory acute KD. However, given the limited data and risks of these agents, use should be reserved for patients for which other modalities have failed.[9]

Cyclophosphamide

MOA: The liver converts CYC into phosphoramide mustard, which stops cell division by creating irreversible DNA cross-links. By inhibiting immune cells, this causes cell death and lowers inflammation.

DOSING: 2mg/kg/d IV.[1]

SIDE EFFECTS: Abdominal pain, nausea, vomiting, loss of appetite, diarrhea, hair loss.

TREATMENT OF THE CARDIOVASCULAR COMPLICATIONS OF KAWASAKI DISEASE

Coronary artery aneurysms (CAAs) are the primary complication associated with Kawasaki disease. About half of these aneurysms resolve within a few years. Specifically, a pseudo-normalization of the luminal dimensions is seen within 1–2 years for small aneurysms and in approximately 80% of medium-sized ones within five years. However, the repair process can lead to stenosis in the areas surrounding the aneurysm due to intimal hyperplasia or thrombotic occlusion, which poses risks of myocardial ischemia, heart attacks, and sudden death.[4]

Platelet activation is essential during all stages of Kawasaki disease. Consequently, for patients with persistent CAAs, a long-term regimen of low-dose aspirin[4] (3–5 mg/kg/day, with a maximum of 81–325 mg) is advised.[1] This may be supplemented with other antiplatelet agents, anticoagulants, or anti-anginal medications depending on the size of the aneurysms, blood flow characteristics, and the presence of myocardial ischemic changes.[4]

ANTIPLATELET DRUGS

1. Clopidogrel

For certain patients with very severe or complex coronary artery aneurysms at high risk of thrombosis or with evidence of prior thrombosis, as well as moderate coronary artery aneurysms or large or giant aneurysms that have shrunk to moderate size, it is recommended as thromboprophylaxis in conjunction with ASA and anticoagulation (triple therapy). If the patient is allergic to ASA, it can be used as a substitute for ASA.

MOA: By attaching itself to the platelet P2RY12 purinergic receptor, the thienopyridine derivative clopidogrel stops platelets from clumping together. This stops platelet activation caused by ADP.

DOSING: In children younger than 24 months, low doses of clopidogrel (0.2 mg/kg/day) typically produce an antiplatelet effect. Children older than 25 months should take 1 mg/kg per day; adults should take no more than 75 mg per day.[4]

SIDE EFFECTS: clopidogrel include malaise, headache, dizziness, myalgia, gastro intestinal symptoms, rash, itching, bleeding tendency and thrombotic thrombocytopenic purpura.[4]

2. Dipyridamole

If the patient is allergic to or resistant to ASA, it can be used in its place.

MOA: Dipyridamole is a platelet inhibitor that raises cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP) levels by blocking phosphodiesterase and adenosine deaminase. Platelet aggregation and thrombosis are inhibited by these elevated cAMP and cGMP levels.

DOSING: oral administration of 1–5 mg/kg/d.[1]

SIDE EFFECTS: headache, flushing, diarrhoea, rash, itching, disorientation, and stomach pain.

3. Abciximab

Limited use, often administered as a single course to individuals with coronary artery aneurysms who experience occlusive and nonocclusive thrombosis.

MOA: By attaching itself to platelet GP2b/3a receptors, it stops platelets from aggregating.

DOSING: 0.125 µg/kg/min every 12 hours after a 0.25 mg/kg bolus.[1]

SIDE EFFECTS: blurred vision, sweating, unusual weakness or fatigue, confusion, bleeding, lightheadedness, fainting, or dizziness when abruptly rising from a sitting or reclining posture.

ANTICOAGULANT THERAPY

1. UFH

MOA: Antithrombin III is activated, and it binds to clotting factor to produce an anticoagulant action.

DOSING: Age-dependent dosage: 28 U·kg/h ≥12 months of age: 20 U·kg/h

Low dose: typically between 10 and 15 U·kg/h Adjust to the PTT goal range. administered as an ongoing parenteral infusion.

Range of targets: Depending on local laboratory data, anti-factor Xa (0.35-0.70 U/mL) and PTT 1.5-3 times

baseline PTT should be checked at least every 24 hours.[1,17]

SIDE EFFECTS: thrombocytopenia, diarrhoea, dermatitis, hepatic dysfunction, haemorrhage, and hair loss.[4]

2. LMWH

For patients with big or enormous coronary artery aneurysms or a history of thrombosis, especially in young newborns or those with enlarging aneurysms early in their illness, chronic thromboprophylaxis is an alternative; for patients, it serves as a bridge between UFH and warfarin.

LMWHs attach to factor Xa and catalyse its inactivation, while MOA activates antithrombin III, which subsequently binds to clotting factor.

Anti-factor Xa level should be monitored at least once a month, with a target range of 0.5 to 1.0U/mL.

SIDE EFFECTS: thrombocytopenia, diarrhoea, dermatitis, hepatic dysfunction, and haemorrhage.[4]

A) Enoxaparin

DOSING: Subcutaneously administered every 12 hours: 1.0 mg/kg per dose at 2 months of age in newborns, higher dosages can be required; titrate to the anti-factor Xa target range. Get levels 4-6 hours after the dose.

B) Tinzaparin

DOSING: Given every 24 h subcutaneously: 0–2 mo: 275 U/kg per dose 2–12 mo: 250 U/kg per dose 1–5 y: 240 U/kg per dose 5–10 y: 200 U/kg per dose >10 y: 175 U/kg per dose Titrate to anti–factor Xa target range. Age-dependent monitoring: < 5 y: 2 h after dose, ≥ 5 y: 4 h after dose.

3. Warfarin

Patients who have had prior thrombosis or massive or enormous coronary artery aneurysms should receive long-term thromboprophylaxis.

MOA: The vitamin K epoxide reductase complex subunit 1 (VKORC1), an enzyme necessary for activating accessible vitamin K, is competitively inhibited by warfarin. Warfarin can decrease the generation of active clotting factors by using this method to deplete functional vitamin K stores.

DOSAGE: First, load 0.2 mg·kg/d, followed by 0.1 mg·kg/d; titrate the dose to INR target level (2–3). Check INR every day until it falls into the target range, and then at least once a month. Test INR while you're sick, taking medicine, or changing your diet.[1,17]

SIDE EFFECTS: bleeding (epistaxis, intracranial, gum bleeding, and intra-abdominal haemorrhage), embryopathies (dyschondroplasia, microcephaly, and dysostosis).[1,4]

THROMBOLYTIC THERAPY

Alteplase

Reserved for people who have thrombosis from coronary artery aneurysms.

MOA: When alteplase binds to fibrin on a clot's surface, it changes plasminogen into plasmin, which disintegrates the fibrin molecules and dissolves the clot.

DOSING: 0.1–0.6 (usually 0.5) mg·kg/h IV for 6 hours, especially if occlusive 0.2 mg/kg IV bolus (maximum 15 mg), 0.75 mg/kg over 30 min (maximum 50 mg), and 0.5 mg/kg over 60 min (maximum 35 mg) for a maximum dose of 100 mg, in accordance with adult guidelines.[1,17]

After the infusion is finished, reevaluate the thrombus using imaging; retreatment might be necessary until the haematologic parameters are adequate; close patient monitoring is necessary, and any indication of internal bleeding should be promptly investigated.

SIDE EFFECTS: bleeding due to a puncture, bleeding gums, difficulty with breathing or swallowing, headache, coughing up blood, increased menstrual flow or vaginal bleeding and nosebleeds.

NON PHARMACOLOGICAL TREATMENT OF CORONARY ARTERY THROMBOSIS

Interventional catheterization procedures face challenges due to the large delivery systems used for small patients, a high risk of complications, and limited effectiveness, which can lead to a significant chance of needing reintervention. Coronary artery reperfusion through both invasive cardiology interventions and cardiac surgery may be considered following an unsuccessful initial pharmacological thrombolysis. Cardiological options include percutaneous thrombolysis, percutaneous angioplasty, and rotational ablation.[1, 19]

FOLLOW UP AND LONG TERM MANAGEMENT OF KAWASAKI DISEASE

Long-term management starts at the conclusion of the acute phase, typically 4 to 6 weeks after the onset of fever, once symptoms have resolved and the extent of coronary artery involvement has reached its peak. The primary objectives of long-term management are to prevent thrombosis and myocardial ischemia while promoting optimal cardiovascular health. While there are no specific treatments targeting the ongoing subacute or chronic vasculitis and luminal dimension changes in patients with coronary artery aneurysms, statins may have a potential role in this context.[16,18] Key components of management include thromboprophylaxis and vigilant monitoring for coronary artery stenosis, obstructions, and myocardial ischemia. For selected patients experiencing myocardial ischemia, revascularization through catheter interventions,

coronary artery bypass surgery, or, in rare cases, cardiac transplantation may be considered.[1]

CARDIAC RISK LEVELS AND LONG-TERM MANAGEMENT

1. If no coronary artery aneurysm: Although continuous follow-up up to 12 months may be considered, it is appropriate to release patients from cardiology care 4–6 weeks after the commencement of KD. Continuous follow-up in cardiology is not recommended. At least once, and preferably within a year of the acute KD episode, measure blood pressure, fasting lipid profile, body mass index, waist circumference, dietary and activity assessment, and smoking. After the acute KD episode, administer low-dose ASA for up to 4–6 weeks; after that, it should be stopped.[1]

2. Small aneurysm: It is permissible to evaluate patients six months and a year after the acute KD episode, however patients should be evaluated four to six weeks later. It is reasonable to conduct a follow-up assessment annually after that. Every two to three years, or if the patient exhibits symptoms suggestive of ischaemia or signs suggestive of ventricular dysfunction, it is reasonable to check for inducible myocardial ischaemia using stress echocardiography, stress with magnetic resonance imaging [MRI], stress nuclear medicine [NM], and positron emission tomography [PET]. Every three to five years, further imaging with angiography (CT, MRI, invasive) may be taken into consideration for periodic surveillance. For non-lipid-lowering (pleiotropic) effects, empirical statin medication may be taken into consideration. Patients should get low-dose ASA treatment, and clopidogrel therapy if they are ASA resistant.[1]

3. Medium size aneurysm: It is permissible to evaluate patients three, six, and one year following the acute KD event, although patients should be evaluated four to six weeks later. It is normal to conduct follow-up assessments every six to twelve months after that. Using stress echocardiography, stress with MRI, stress NM perfusion imaging, and PET, check for inducible myocardial ischaemia every one to three years, or if the patient exhibits symptoms of ischaemia or indications of ventricular dysfunction. Every two to five years, further angiography imaging (CT, MRI, invasive) may be recommended for periodic surveillance. Consideration may be given to statin, ASA, and dual-antiplatelet therapy in addition to an additional antiplatelet drug (such as a thienopyridine like clopidogrel). For patients taking dual-antiplatelet therapy, activities involving a risk of bodily contact, trauma, or injury should be restricted or modified.[1]

4. Gaint aneurysm: It is advisable to evaluate patients at 3, 6, 9, and 12 months following an acute Kawasaki disease episode during the first year, and then every 3 to 6 months thereafter. Assessments for inducible myocardial ischemia—using methods like stress echocardiography, MRI with stress, stress nuclear perfusion imaging, or PET—should occur every 6 to 12 months, or if the patient exhibits symptoms of ischemia or signs of ventricular dysfunction. Further imaging with angiography (CT, MRI, or invasive methods) may be warranted for diagnostic and prognostic purposes within the first year and could also be used for periodic surveillance every 1 to 5 years afterward. Empirical statin therapy for its non-lipid-lowering (pleiotropic) effects may be considered. Patients should receive low-dose aspirin, with clopidogrel prescribed if they are resistant to aspirin. Warfarin may be used to maintain a target international normalized ratio of 2 to 3, while low molecular weight heparin (LMWH) can be an alternative to achieve target anti-factor Xa levels of 0.5 to 1.0 U/mL. In cases of extensive or distal coronary artery aneurysms, or a history of coronary artery thrombosis, adding another antiplatelet agent (such as clopidogrel) to the combination of aspirin and warfarin/LMWH (triple therapy) for thromboprophylaxis may be considered. Additional characteristics of the patient and coronary arteries should guide decisions on adjustments to thromboprophylaxis strategies. Activities that pose a risk of contact, trauma, or injury should be restricted or modified.[1]

ONGOING CLINICAL TRIALS

1. Atorvastatin

Statins have been linked to antioxidant and anti-inflammatory properties, especially when it comes to lowering inflammatory indicators like CRP. [14] According to a PK/Safety Study of Atorvastatin in Children with KD and CAA, statins' anti-inflammatory, antioxidant, and endothelial-healing qualities may help prevent the advancement of coronary artery anomalies in KD 15. Furthermore, a clinical trial is presently being recruited in China for the adjuvant use of statins in children with significant CA anomalies.[9]

2. Doxycycline

One antibiotic that suppresses matrix metalloproteinase-9 (MMP-9) is doxycycline. MMP-9 may be a major factor in the development of CAA.[39] and has been detected at elevated serum levels during acute KD. Doxycycline is presently being recruited for a phase II research to evaluate its safety and effectiveness in halting the development and progression of coronary artery aneurysms.[9]

CONCLUSION

In order to effectively treat Kawasaki Disease (KD) and associated cardiovascular complications, especially coronary artery aneurysms (CAAs), and prevent long-term consequences, a multimodal strategy is necessary. Aspirin and high-dose intravenous immune globulin (IVIG), which together lower inflammation and prevent thrombosis linked to CAAs, are part of the main therapeutic regimen. Alternative therapies such corticosteroids, infliximab, cyclosporine, and anakinra

may be used for patients who are not responding to the first IVIG therapy; however, their effectiveness in treating refractory cases varies.

Careful monitoring and the administration of antiplatelet and anticoagulant treatments are essential for the management of KD, especially when there are notable coronary artery anomalies. Medications such as low-dose aspirin, clopidogrel, and anticoagulants like unfractionated heparin and low molecular weight heparin play critical roles in preventing thrombotic events in patients with CAAs. For acute thrombosis in CAAs, thrombolytic therapy with drugs like alteplase may be used; nevertheless, close observation for bleeding consequences is crucial.

Moreover, KD's effects linger beyond its immediate cure, requiring continuous monitoring of cardiovascular health and suitable treatments, such as non-pharmacological methods like catheterisation or surgery in situations that don't improve. In order to maximise patient outcomes and reduce the risks of myocardial ischaemia and other cardiovascular events, it is imperative to implement evidence-based strategies that address both the acute and chronic consequences of KD as research advances. In order to manage the complications of Kawasaki Disease and its long-term effects on cardiovascular health, paediatric cardiologists, immunologists, and primary care physicians must collaborate.

REFERENCE

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation, 2017 Apr 25; 135(17): e927-99.
2. Burns JC, Franco A. The immunomodulatory effects of intrave nous immunoglobulin therapy in Kawasaki disease. Expert Rev Clin Immunol., 2015; 11: 819–825. doi: 10.1586/1744666X. 2015.1044980.
3. Kuo HC. Diagnosis, Progress, and treatment update of Kawasaki Disease. International Journal of Molecular Sciences, 2023 Sep 11; 24(18): 13948.
4. Marchesi A, Tarissi de Jacobis I, Rigante D, Rimini A, Malorni W, Corsello G, Bossi G, Buonuomo S, Cardinale F, Cortis E, De Benedetti F. Kawasaki disease: guidelines of Italian Society of Pediatrics, part II-treatment of resistant forms and cardiovascular complications, follow-up, lifestyle and prevention of cardiovascular risks. Italian Journal of Pediatrics, 2018 Dec; 44: 1-8.
5. Hedrich CM, Schnabel A, Hospach T. Kawasaki disease. Frontiers in paediatrics, 2018 Jul 10; 6: 198.
6. Rowley AH, Shulman ST. The epidemiology and pathogenesis of Kawasaki disease. Frontiers in paediatrics, 2018 Dec 11; 6: 374.
7. Singh S, Jindal AK, Pilania RK. Diagnosis of Kawasaki disease. International journal of rheumatic diseases, 2018 Jan; 21(1): 36-44.
8. Rife E, Gedalia A. Kawasaki disease: an update. Current Rheumatology Reports, 2020 Oct; 22: 1-0.
9. Zhu F, Ang JY. 2021 update on the clinical management and diagnosis of Kawasaki disease. Current infectious disease reports, 2021 Mar; 23: 1-1.
10. Owens AM, Plewa MC. Kawasaki disease, https://www.ncbi.nlm.nih.gov/books/NBK537163
11. Kim GB. Reality of Kawasaki disease epidemiology. Korean journal of paediatrics, 2019 Aug; 62(8): 292.
12. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. Archives of disease in childhood, 2015 Nov 1; 100(11): 1084-8.
13. Pilania RK, Basu S, Dixit J, Kumrah R, Jindal AK, Thangaraj A, Nimesh R, Kaur T, Vignesh P, Suri D, Rawat A. Incidence of Kawasaki disease among children in Chandigarh, India during 2015–2019: a trend analysis. The Lancet Regional Health-Southeast Asia. 2024 Oct 1; 29.
14. RidkerPM, RifaiN, PfefferMA, SacksFM, MoyeLA, GoldmanS, et al. Inflammation, pravastatin, and the risk of coronaryevents after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation, 1998; 98(9): 839–44.
15. Tremoulet AH. The role of statins in inflammatory vasculitides. Autoimmunity, 2015; 48(3): 177–80.
16. Blankier S, McCrindle BW, Ito S, Yeung RS. The role of atorvastatin in regulating the immune response leading to vascular damage in a model of Kawasaki disease. Clin Exp Immunol., 2011; 164: 193 201. doi: 10.1111/j.1365-2249.2011.04331.x.
17. Giglia TM, Massicotte MP, Tweddell JS, Barst RJ, Bauman M, Erickson CC, Feltes TF, Foster E, Hinoki K, Ichord RN, Kreutzer J, McCrindle BW, Newburger JW, Tabbutt S, Todd JL, Webb CL; on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Stroke Council. Prevention and treatment of throm bosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association [published correction appears in Circulation., 2014; 129: e23]. Circulation. 2013; 128: 2622–2703. doi: 10.1161/01.cir.0000436140.77832.7a.
18. Orenstein JM, Shulman ST, Fox LM, Baker SC, Takahashi M, Bhatti TR, Russo PA, Mierau GW, de Chadarévian JP, Perlman EJ, Trev enen C, Rotta AT, Kalelkar MB, Rowley AH. Three linked vasculo pathic processes characterize Kawasaki disease: a light and trans mission electron microscopic study. PLoS One, 2012; 7: e38998. doi: 10.1371/journal.pone.0038998.
19. Rowley AH, Baker SC, Shulman ST, Fox LM, Takahashi K, Gar cia FL, Crawford SE, Chou P,

Orenstein JM. Cytoplasmic inclu sion bodies are detected by synthetic antibody in ciliated bron chial epithelium during acute Kawasaki disease. J Infect Dis., 2005; 192: 1757–1766. doi: 10.1086/497171.
20. TremouletAH, JainS, Jaggi P, Jimenez-Fernandez S, PancheriJM, Sun X, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo controlled trial. Lancet, 2014; 383(9930): 1731–8.
21. Miura M, Ohki H, Yoshiba S, Ueda H, Sugaya A, Satoh M, et al. Adverse effects of methylprednisolone pulse therapy in refractory Kawasaki disease. Arch Dis Child., 2005; 90: 1096–7.
22. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. Cyclooxygenase in hibitors and the antiplatelet effects of aspirin. N Engl J Med., 2001; 345: 1809–1817. doi: 10.1056/NEJMoa003199.
23. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intra venous gamma globulin. N Engl J Med., 1986; 315(6): 341–7.
24. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet, 1984; 2(8411): 1055–8.
25. Durongpisitkul K, Gururaj VJ, ParkJM, MartinCF. Theprevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics., 1995; 96(6): 1057–61.
26. Vervoort D, Donné M, Van Gysel D. Pitfalls in the diagnosis and management of Kawasaki disease: An update for the pediatric dermatologist. Pediatr Dermatol., 2018 Nov; 35(6): 743-747.
27. Sundel RP. Kawasaki disease. Rheum Dis Clin North Am., 2015; 41(1): 63-73, viii.
28. Marchesi A, Tarissi de Jacobis I, Rigante D, Rimini A, Malorni W, Corsello G, Bossi G, Buonuomo S, Cardinale F, Cortis E, De Benedetti F, De Zorzi A, Duse M, Del Principe D, Dellepiane RM, D'Isanto L, El Hachem M, Esposito S, Falcini F, Giordano U, Maggio MC, Mannarino S, Marseglia G, Martino S, Marucci G, Massaro R, Pescosolido C, Pietraforte D, Pietrogrande MC, Salice P, Secinaro A, Straface E, Villani A. Kawasaki disease: guidelines of the Italian Society of Pediatrics, part I - definition, epidemiology, etiopathogenesis, clinical expression and management of the acute phase. Ital J Pediatr., 2018 Aug 30; 44(1): 102.
29. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E., American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation., 2017 Apr 25; 135(17): e927-e999.
30. Kawasaki T Acute febrile mucocutaneous syn drome with lymphoid involvement with specific desqua mation of the fingers and toes in children. Arerugi Allergy, 1967; 16: 178–222.
31. RodoX, Curcoll R, RobinsonM, Ballester J, Burns JC, Cayan DR, et al. Tropospheric winds from northeastern China carry the etio logic agent of Kawasaki disease from its source to Japan. Proc Natl Acad Sci U S A., 2014; 111(22): 7952–7.
32. McCrindle, B.W.; Rowley, A.H.; Newburger, J.W.; Burns, J.C.; Bolger, A.F.; Gewitz, M.; Baker, A.L.; Jackson, M.A.; Takahashi, M.; Shah, P.B.; et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation, 2017; 135: e927–e999.
33. Ayusawa, M.; Sonobe, T.; Uemura, S.; Ogawa, S.; Nakamura, Y.; Kiyosawa, N.; Ishii, M.; Harada, K. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr. Int., 2005; 47: 232–234. [CrossRef] [PubMed] Gong, G.W.; McCrindle, B.W.; Ching, J.C.; Yeung, R.S. Arthritis presenting during the acute phase of Kawasaki disease. J. Pediatr., 2006; 148: 800–805.
34. Terasawa K, Ichinose E, Matsuishi T, et al. Neurological complications in Kawasaki disease. Brain Dev., 1983; 5(4): 371–4.
35. Latino GA, Manlhiot C, Yeung RSM, et al. Macrophage activation syndrome in the acute phase of Kawasaki disease. J Pediatr Hematol Oncol., 2010; 32(7): 527–31.
36. Watanabe T. Pyuria in patients with Kawasaki disease. World J Clin Pediatr., 2015; 4(2): 25–9.
37. Gong GWK, McCrindle BW, Ching JC, et al. Arthritis presenting during the acute phase of Kawasaki disease. J Pediatr., 2006; 148(6): 800–5.
38. Uziel Y, Hashkes PJ, Kassem E, et al. "Unresolving pneumonia" as the main manifestation of atypical Kawasaki disease. Arch Dis Child., 2003; 88(10): 940–2.
39. Senzaki H. The pathophysiology of coronary artery aneurysms in Kawasaki disease: role of matrix metalloproteinases. Arch Dis Child., 2006; 91(10): 847–51.
40. Glazyrina A, Kurbanova S, Kantemirova M, Novikova Y, Ovsyannikov D, Zholobova E, Valieva S, Petryaykina E. AB0980 efficacy of etanercept treatment for children with kawasaki disease intractable to intravenous immunoglobulin therapy in russian children.