CORPUS PUBLISHERS

Global Journal of Pediatrics (GJP)

Volume 2, Issue 1, 2022

Article Information

Received date : December 21, 2021

Published date: January 10, 2022

*Corresponding author

Lei Sun, Department of Pediatrics, Chang'an Hospital, Xi'an, China

Key Words

Kawasaki Disease; Atypical Kawasaki Disease; Diagnosis; Treatment

Abbreviations

KD: Kawasaki Disease; IVIG: Immunoglobulin; AHA: American Heart Association; MAS: Macrophage Activation Syndrome; KDSS: Kawasaki Shock Syndrome; PE: Plasma Exchange; ASA: Aspirin; PGE2: Prostaglandin E2; TXA2: Thromboxane A2; HIT: Heparin-Induced Thrombocytopenia

Research Article

Update of Diagnosis and Treatment in Atypical Kawasaki Disease

Hui Wen[1], Lei Sun[2], Juan liu[3*] and Weihua Zhang[3]

[1]*Dept of Pediatrics, Changan Hospital, China*

[2]*Dept of Pediatrics, the Hospital of Shenmu city (Shenmu Hospital Affiliated to Northwest University), China*

[3]*Children's Hospital of Xianyang City ,Shaanxi ,China*

Abstract

Kawasaki Disease (KD) is an unknown etiology of systemic small vasculitis as the main lesion of acute febrile extranuclear disease, mainly affecting children under five years old, is also the main disease causing acquired heart disease in children. Its etiology is unknown but it is thought to be related to genes, infection and immunity. In particular, the diagnosis and treatment of atypical Kawasaki disease is a major clinical challenge. This paper reports the progress of the treatment of atypical Kawasaki disease, including the causes, clinical manifestations, diagnosis and treatment of Kawasaki disease, especially the progress of drug therapy in recent years.

Introduction

Kawasaki Disease (KD) is a systemic multi-system inflammation of blood vessels, the cause of which is still unclear, but it is believed to be related to immune, infection and genetic factors. It was first reported by Tomisaku Kawasaki in 1967. Kawasaki disease is an acute febrile rash disease with systemic vasculitis as the main lesion and usually occurs in infants under 5 years old. Studies in Japan and China suggest that the incidence of Kawasaki disease is increasing, and it has become one of the common inpatient diseases of pediatrics in China. Kawasaki disease are the main hazards of coronary artery complications, although the Immunoglobulin (IVIG) therapy, the incidence is still up to 3~7%, especially coronary artery giant tumors may be due to tumor rupture or tumor thrombus in death, the forward more coronary artery stenosis or occlusion cause heart failure or sudden death, long-term prognosis is poor, has replaced rheumatic fever become one of the most common causes of acquired heart disease of children, Seriously harm the physical and mental health of children, children's families and society caused a burden. Due to the unclear etiology and pathogenesis of Kawasaki disease, clinical diagnosis is mainly based on the clinical manifestations of children. However, many children have atypical clinical manifestations, which is called incomplete Kawasaki disease. Clinically, these children are often delayed due to missed diagnosis or misdiagnosis. The use of IVIG 10 days after onset was found to be the largest independent risk factor for KD coronary aneurysm, so early and accurate diagnosis has an important impact on the prognosis of Kawasaki disease. In addition, in recent years, it has been found that some children have no obvious effect on conventional IVIG treatment, which is called IVIG resistance. The incidence of coronary complications in children with IVIG resistance is more than 10 times higher than that in patients with IVIG sensitivity, and the incidence is also increasing. Therefore, early screening of children who may develop IVIG non-response and timely and reasonable treatment is also an urgent clinical topic to be solved. In many countries, Kawasaki disease has become the main cause of acquired heart disease, and its incidence rate is increasing year by year. The typical clinical manifestations of Kawasaki disease are in the acute phase of the disease, including fever, bilateral non-exudative conjunctivitis, erythema of lip and oral mucosa, limb lesions, rash and cervical lymph node enlargement. In addition to causing coronary artery damage such as coronary dilation and coronary aneurysm, myocarditis, valve regurgitation, Kawasaki shock syndrome, pulmonary nodules, arthritis, hepatitis, urethritis and other diseases can also be caused [1]. Existing studies strongly suggest that KD is immune-mediated, genetically related, infection-induced and multi-system involved pediatric cardiovascular disease. With the improvement of diagnosis and treatment technology and changes in human living environment, the incidence of KD is increasing year by year, especially in Countries with high incidence in Asia, such as Japan and South Korea. The incidence of Kawasaki disease increased to 107.3 per 100,000 in Shanghai from 1998 to 2017 [1-3]. The diagnosis and treatment of Kawasaki disease is still a challenge for clinicians and nursing staff, especially for pediatricians, community non-pediatric specialists or medical staff who lack experience in the diagnosis and treatment of Kawasaki disease. The diagnosis of atypical Kawasaki disease is more complex because the symptoms appear at an atypical time and often do not occur at multiple times. Therefore, clinicians need to be aware of the epidemiology and clinical manifestations of the disease, as well as the latest methods and knowledge of diagnosis and treatment.

Pathogeny

Many bacteria or viruses have been reported to be associated with Kawasaki disease, but no definitive conclusion has been reached. Recently, human coronavirus has been reported in the United States (ES-per et al., 2005) that there is a strong correlation between kawasaki disease and human coronaviruses. However, the rapid response of Kawasaki disease to a single high dose of immunoglobulin can also indicate that the host immune response is more important than the role of the infectious agent if the good results of immunoglobulin treatment are seen. Therefore, according to the known evidence, Kawasaki disease may be caused by the infection of some non-specific pathogen, causing the host with a specific constitution to produce excessive or maladjusted immune response, and then causing systemic inflammation of blood vessels.

The Clinical Manifestations of Atypical Kawasaki Disease

The diagnostic criteria for Kawasaki disease are as follows [1-2], fever lasts for at least five days and meets at least five other criteria for typical Kawasaki disease: (-) bilateral conjunctivitis (non-purulent and painless, Is often violated eye conjunctiva parts), (2 diffusivity of mucous membrane inflammation (swelling of the oral mucosa and strawberry tongue and lips red dryness), yan, polymorphous skin rash (limbs and torso will appear such as urticaria, rash, pimples, erythema multiforme and relatively rare small pustular rash), looking limb, hyperemia dropsy, and unilateral neck lymph node enlargement

lesions (usually greater than 1.5 Cm). Other common clinical symptoms of Kawasaki disease are as follows: cardiovascular aspects (coronary artery disease: vascular dilation, arterial fistula, coronary aneurysm, myocardial infarction and myocarditis); Musculoskeletal (arthritis, arthralgia); Gastrointestinal tract (abdominal pain, vomiting, diarrhea, abnormal liver function, gallbladder edema and pseudo intestinal obstruction); Central nervous system [irritability, aseptic meningitis, sensory nerve hearing loss and transient cerebral vascular ischemia]; Urological system (pyuria or urethritis); Other aspects (redness or ulceration at BCG site, mild anterior uveitis and anal peeling). The acute phase laboratory findings are as follows: Neutrophilic pleocytosis in white blood cells and the formation of immature cells, elevated blood sedimentation, elevated c-reactive protein, anemia, dyslipidemia, low serum albumin leels, hyponatremia, a week after the plaque but some babies thrombocytopenia and diffuse intravascular coagulation, sterile pyuria, serum transaminase (SGPT and SGOT) increased, serum C bran amine acyl transfer GGT increased and cells in cerebrospinal fluid increased. However, in recent years, there are many symptoms similar to Kawasaki disease, but they cannot fully meet the diagnostic criteria, we call it atypical or incomplete KD. The diagnosis of atypical Kawasaki disease is based on sustained fever for more than 5 days, and the incisions are less than 3. Plus coronary artery disease; It usually occurs in children under one year of age, or over five years of age, and accounts for approximately 15% of all Kawasaki disease. Assess suspected atypical or incomplete Kawasaki disease as recommended by the American Heart Association (AHA) [8]. It must also be differentiated from other infectious or noninfectious diseases such as toxic shock syndrome, scarlet fever, Stephen Johnson syndrome, juvenile rheumatoid arthritis, and adenovirus infection.

Diagnostic

The Japanese Committee for The Study of Cutaneous and Mucosal Lymph Node Syndrome (1984) proposed that the diagnostic criteria for this disease should be determined by meeting at least five of the following six main clinical symptoms:

a) Fever of unknown cause, lasting for 5 days or more,

b) Bilateral conjunctiva hyperemia,

c) Oral and pharyngeal mucosa diffuse hyperemia, lips red and dry, and bayberry tongue,

d) At the beginning of the disease, hand and foot swelling and palm and metatarsal redness, as well as the recovery of the toe membrane peeling; The trunk is erythema multiform, but without blister or scab,

e) Non-suppurative swelling of the neck lymph node, with a diameter of 1.5cm or greater.

However, if a coronary aneurysm or dilation is detected by two-dimensional echocardiography or coronary angiography, a positive diagnosis can be made for all four major symptoms. The number of incomplete or atypical cases is increasing, about 10% ~ 20%. There are only 2~3 main symptoms, but there are typical coronary artery lesions. Most often in infants. The incidence of coronary aneurysms in typical and atypical cases was similar. Once Kawasaki disease is suspected, echocardiography should be done as soon as possible.

Auxiliary Examination

In acute stage, the total number of leukocytes and the percentage of granulocytes increased, and the nucleus shifted left. Mild anemia was seen in more than half of the patients. The esR increased significantly, and the esR reached more than 100mm in the first hour. Serum protein concentration increased, especially α_2 globulin. Albumin decreases. IgG, IgA, IgA increased. Platelets begin to increase at week 2. The blood is hypercoagulable. The titer of antistreptohaemolysin O was normal. Rheumatoid factor and ant nucleosome were negative. C-reactive protein increased. Serum complement is normal or slightly high. Urine sediment shows leukocytosis and/or proteinuria. Ecg can see a variety of changes, ST segment and T wave abnormality is more common, can also show P-R, Q-R interphase prolonged, abnormal Q and arrhythmia. Two-dimensional echocardiography is suitable for cardiac examination and long-term follow-up. In half of the cases, various cardiovascular lesions such as pericardial effusion, left ventricular enlargement, mitral valve insufficiency, coronary artery dilation or aneurysm formation can be found. It is the most reliable noninvasive method for monitoring coronary aneurysms, preferably once a week during the acute and subacute phases of the disease. In cases of aseptic meningitis, CSF lymphocytes can be as high as 50-70 /mm^3. In some cases, slightly higher levels of serum bilirubin or glutamine may be seen. Both bacterial culture and virus isolation showed negative results [4-6].

The Differential Diagnosis

It should be identified with all kinds of infectious diseases, viral infection, acute lymphadenitis, rheumatoid diseases and other connective tissue diseases, viral myocarditis, rheumatism and carditis. The differences between this disease and scarlet fever are as follows:

a) The rash does not begin until the third day after the onset,

b) The appearance of the rash was similar to measles and erythema multiform,

c) The onset age is infants and young children,

d) Penicillin has no effect.

The differences between this disease and juvenile rheumatoid diseases are as follows:

a) The fever period is shorter and the rash is shorter,

b) Hands and feet are hard and swollen, showing constant zhi flushing,

c) Rheumatoid factor was negative.

The differences with erythema multiform with effusion are as follows:

a) There is no purulent secretion and pseudo membrane formation in eyes and lips;

b) The rash does not include blisters and scabs.

The differences with systemic lupus erythematosus are as follows:

a) The rash is not significant on the face,

b) The total number of white blood cells and platelets generally increased,

c) Antinuclear antibody was negative,

d) The age of good hair is infants and boys.

The symptoms of infantile nodular poly arteria have many similarities, but the incidence of cutaneous and mucous lymph node syndrome is more, the course of disease is shorter, and the prognosis is better. The relationship between the two diseases remains to be studied.

The difference with erupting virus infection is:

a) lip flushing, dry crack, bleeding, bayberry tongue,

b) Hard swelling of hands and feet, often zhi flushing and late appearance of toe membrane peeling,

c) No edema or secretion in conjunctiva,

d) The total number of white blood cells and the percentage of granulocytes increased, accompanied by left nuclear shift,

e) EsR and C-reactive protein were significantly increased.

The differences with acute lymphadenitis are as follows:

a) Cervical lymph node enlargement and tenderness are lighter, local skin and subcutaneous tissue have no swelling,

b) No purulent lesions.

The differences with viral myocarditis are as follows:

a) prominent coronary artery lesions,

b) Characteristic hand-foot changes,

c) High fever does not retreat.

The differences with rheumatic carditis are as follows:

a) Prominent coronary artery lesions,

b) No significant heart murmur,

c) The age of onset was mainly infants.

Kawasaki disease do not having a gold standard in diagnosis of atypical clinical manifestations and no specific laboratory diagnosis index, the misdiagnosis rate is high, such as the common cold, sepsis, drug allergy, scarlet fever, measles, adenoviruses infection, easily misdiagnosed, and missed the best period of treatment, and concurrent coronary artery damage easily. Therefore, early diagnosis and treatment, It is very important to reduce the incidence of heart disease in children. The elevation of ferritin has other significance, which should be identified. Elevated ferritin suggests the diagnosis of systemic juvenile idiopathic arthritis, macrophage activation syndrome, hemophilic cell syndrome, malignancy, iron overload, and viral infection. Unexplained inflammatory responses are considered infections, hematologic diseases, tumors, and rheumatoid immune diseases.

The Treatment

Kawasaki disease is currently treated with a single high dose of intravenous immunoglobulin (2 gm/Kg/dose) combined with aspirin within five to ten days of fever [6-9].

Intravenous immunoglobulin (IVIG)

IVIG is the safest and most reliable treatment available, and its efficacy is recognized worldwide and described in many textbooks and guidelines. The most reliable anti-inflammatory treatment for acute KD is early high-dose injection of intact immunoglobulin, which can prevent CAA complications [6]. IVIG indications are present in almost all patients with acute KD who typically meet the diagnostic guidelines (6th edition) and are at risk for CAA complications. A small number of patients with mild symptoms or spontaneous resolution of fever were not treated with IVIG according to each facility's severity criteria. The dosage was divided into single-dose regimen (2 g/kg/ day) and multiple-dose regimen (200-400 mg/kg/ day, 3-5 days). A large number of clinical data proved that single-dose regimen significantly reduced the incidence of CAA, reduced adverse markers earlier, and had a higher antipyretic effect.

Mechanism of action

GC has been widely used in the treatment of vasculitis with remarkable effect. GC was used as the initial treatment of KD long before IVIG therapy was first reported by Furusho et al in 1984. The mechanism of GC regulating inflammatory response is the result of the pleiotropic effect of GC receptor on various signaling pathways. Many molecular pathways are involved in the pathogenesis of KD aneurysm formation, indicating many potential pathways by which GC regulates aneurysm development. Research on the exact mechanism of action is ongoing, and the current theory is that KD pathogenesis involves the immune response of infectious factors. GC can reduce the transcription of inflammatory mediators and reduce the fever and inflammation levels of KD patients, thus reducing the incidence of coronary artery damage and future cardiovascular sequelae [8].

The indications

Including:

a) IVIG no reaction KD,

b) The onset age is less than 1 year,

c) Higher levels of inflammatory markers,

d) Kawasaki Shock Syndrome (KDSS) and KD with Macrophage Activation Syndrome (MAS),

e) CAA exists,

f) Kobayashi's warning score is greater than or equal to 5 points [9-10].

Commonly used drugs

Common drugs for systemic GC include endogenous cortisone and hydrocortisone, as well as exogenous prednisone, prednisolone, methylprednisolone, betamethasone, and dexamethasone. Cortisone and hydrocortisone have the same function as human endogenous corticosteroids. They are short-acting preparations and have both glucocorticoid and salt corticoid activities. Therefore, they are suitable for physiological replacement therapy. Hydrocortisone is more appropriate than cortisone for patients with liver dysfunction. The solvent of hydrocortisone sodium succinate is water, and the solvent of hydrocortisone injection is alcohol. The latter may cause allergic reactions in people allergic to alcohol, and may cause disulphilon-like reactions when used together with some cephalosporin's. Prednisone can strengthen the anti-inflammatory effect, reduce the retention of water and sodium, and prolong the action time. It is a medium-effect preparation, and is the main dosage form for the treatment of autoimmune diseases. Immunosuppression, impact therapy is more suitable for autoimmune diseases, to play a strong immunosuppression, while minimizing side effects. Methylprednisolone is the only drug available for shock therapy. Because its binding rate to the hormone receptor is significantly higher than that of other GC drugs, about 23 times that of prednisone, the onset time is very fast. Therefore, the enzyme activity can be rapidly inhibited and the hormone-specific receptors can be saturated. In addition, methylprednisolone has weak inhibition effect on HPA axis and strong water-solubility, which is easy to reach high plasma concentration. Therefore, it can be used for large dose impact and rapid control of symptoms. Exogenous betamethasone and dexamethasone enhance anti-inflammatory effects and further reduce water and sodium retention. They are long-acting preparations and are only suitable for short-term use, so they are not suitable for treating chronic autoimmune diseases. Therefore, the variety and method of GC treatment for KD patients are methylprednisolone intravenous impulse therapy followed by oral prednisone sequential therapy [6, 11].

Dose and duration

The early warning score was first-line treatment for children with IVIG non-responsive KD or CAA high risk recommended dose: 2 mg/ (kg.d) of prednisone or equivalent amount of methyl prednisone, starting when temperature and C-reactive protein are normal, and phasing out over 15 days [2 mg/ (k.d) for 5 days; 1 mg/(kg.d) for 5 days; 0.5 mg/(kg.d) for 5 days.

For second-line, treatment of IVIG nonreactive KD, a second infusion of IVIG or IVIG combined with prednisone (methylprednisolone) can be selected.

Recommended dose: same as 8.5.1.

First-line treatment of KDSS: Recommended dose: Methylprednisolone 10-30 mg/ (kg.d), 1-3 days.

First-line treatment of KD combined with MASL Recommended dose: Methylprednisolone 10-30 mg/(kg·d), 3 days. Prednisone was given orally sequentially [1-2 mg/ (kg.d)] until remission of MAS was fully controlled and the dosage was gradually reduced.

It is not recommended to use methylprednisolone or prednisone alone as the routine first-line treatment of KD [12-14].

Prevention of adverse reactions

In the treatment of KD in children, special attention should be paid to the prevention of Cushing's syndrome, infection, osteoporosis, aseptic necrosis of femoral head, diabetes, hypertension, steroid-induced glaucoma, cataract, gastrointestinal ulcer bleeding, secondary adrenal cortical insufficiency and growth delay. For the prevention and treatment of osteoporosis, it is suggested to supplement vitamin D 600-800 U/ D and calcium 1 000-1 200 mg/ D during GC treatment. All kinds of infections, especially tuberculosis and fungi, should be fully excluded during high-dose methylprednisolone impact therapy, and blood pressure, blood glucose and other indicators should be monitored closely, so as to find out the above complications in time and actively handle them. In the application of GC at the same time, strive to reduce adverse reactions to the lowest degree, improve the prognosis of KD children.

Steroids

Prednisone (PSL)

The main purpose of PSL therapy is to rapidly solve KD vasculitis and inhibit the potential risk of coronary artery remodeled by utilizing its powerful anti-inflammatory effect [9]. The mechanism is that cytoplasmic steroid receptors inhibit gene transcription of inflammatory proteins, promote gene transcription of anti-inflammatory proteins, and inhibit inflammatory cytokines such as tumor necrosis factor TNF-α, Interleukin IL-6, IL-8, IL-8, G-CSF) chemokines and cell adhesion molecules) and promote the production of anti-inflammatory proteins (such as lip corticosteroids) to inhibit vasculitis and thus have strong anti-inflammatory effects [10]. However, changes in inflammatory markers such as body temperature and

CRP levels during PSL administration may be difficult to determine if the disease has recurred. Therefore, blood tests and echocardiography should be performed regularly during PSL treatment, and appropriate intervention measures should be taken if recurrence is suspected. It should be noted that the most common period of recurrence is 4-5 days after initiation of PSL and after the dose is reduced to 1 mg/kg/d. In principle, second-line PSL regimens should be used in the same way as first-line PSL treatment for non-responders with first-time IVIG. PSL 2mg/(kg.d) was given intravenously in three doses during febrile period. After the patient's condition improves, PSL can be changed to oral administration. In the RAISE regimen, the same dose lasted for five days and was given in three doses for five days after CRP returned to normal. Thereafter, if fever did not recur, the PSL dose would be reduced to 1mg/(kg.d) twice on the subsequent 5 days, and then to a single dose of 0.5 mg/ (kg.d) on the last 5 days. (1, Class A) If the fever recurs after antipyretic, additional treatment should be considered, including increased PSL dose, IVIG retherapy, or other treatments. Although this drug has no obvious side effects, clinicians must monitor sinus bradycardia and adrenal insufficiency caused by PSL [11].

Methylprednisolone pulse (IVMP)

IVMP therapy, namely high-dose intravenous infusion of methylprednisolone, is applied for rapid compression vasculitis based on its powerful and rapid immunosuppression [12]. In KD, IVMP is used to treat people who do not respond to IVIGAS, as an additional rescue therapy, or as a predictor of non-responders to IVIG's initial adjunctive therapy. The effect of IVMP was significant when applied to KD patients, suggesting that non-genomic mechanisms stimulate immune cell activity and inhibit inflammatory cytokines. In patients with confirmed or predicted non-response to IVIG, IVMP has been reported to reduce cytokine production and is transcribed at the genetic level, participating in the development of inflammation and CAA. IVMP is used as a combination therapy for primary IVIGG in patients who are predicted to be non-responders to IVIG, or as an additional rescue therapy in patients who are no responders to IVIG, but it is not included in the safety range of KD. For patients with kidney disease or connective tissue disease, the standard dose of methylprednisolone is 20 to 30mg/kg, given intravenously once daily for 2 to 3 hours for 3 consecutive days. The IVMP regimen reported in previous studies for KD patients was as follows: a single dose of 30mg/kg combined with the first intravenous drip of gamma globulin line, or the same dose given for 1 to 3 consecutive days as an additional rescue treatment for patients who did not respond to 1 vig (class ii a, B). Adverse reactions to the drug included sinus bradycardia (6-82%), hypertension (10-91%), hyperglycemia (6-55%), and hypotension (6-9%). To avoid the development of GASTROINTESTINAL ulcers, patients can take H2 blockers and/or other antacids, and heparin can also be used as a clot prevention agent. However, the need for these drugs has not been proven [13].

Immunosuppressant

Cyclosporine A (CsA)

CsA binds to calcineurin, which plays an important role in signal transduction during the activation of immune cells (including T cells) and inhibits nuclear transport through dephosphorylation of transcription factor NFAT [14]. CsA is indicated for severely ill KD patients at risk for CAA and in combination with early IVIG for predicted non-responders of IVIG or additional treatment of IVIG by non-responders. In February 2020, CsA oral liquid received safety assurance approval for the treatment of KD. For patients who did not respond to IVIG, CsA was taken orally 5mg/(kg·d), divided into 2 times, before meals, in principle for 5 days. The dose of CsA can be changed by measuring the plasma trough concentration before day 3 administration and determining the optimal concentration range between 60 and 200 ng/mL. It is recommended to take before meals to ensure stability of absorption (class ii A, B). For additional treatment in patients who did not respond to IVIG, CsA was given orally in liquid form at 5mg/kg per day in two doses (class ii b, class C). Although no serious side effects of using CsA have been reported so far for Kawasaki disease, it should be noted that asymptomatic hyperkalemia, hypomagraemia, hypertrichosis, etc., should be detected [15].

Methotrexate (MTX)

Low-dose methotrexate (MTX) is effective in inhibiting vasculitis of patients who do not respond to IVIG, and its mechanism of action is not clear, so there is no specific standard for MTX to be used in KD treatment in Japan. MTX orally 10 mg/m² (Max. 16 mg), once a week. In most cases, fever subsided significantly within 24 hours of low-dose MTX administration and CRP levels decreased significantly within 1 week. Side effects often include nausea and vomiting, which is a problem to be solved. So far, there have been no randomized controlled trials, and all traditional studies have been retrospective.

Biological agents

Infliximab (IFX)

IFX is mainly applied in patients who do not respond to IVIG and several enzymes to inhibit inflammatory pathways and compress vasculitis by specifically blocking the action of TNF-α. IFX is primarily used as an additional treatment for patients with acute KD who do not meet standard treatment requirements for non-response to IVIG. Usually 5mg/kg IFX (class ii a,B) is given intravenously. Basically, a single dose of IFX should be used mainly for KD, which is an acute disease, to avoid side effects with frequent use. There is no evidence to recommend the use of IVIG and IFX in all cases of KD. Common adverse reactions include infusion reactions, worsening of infectious diseases (massive tuberculosis and viral hepatitis), aggravation of heart failure, and adverse reactions to vaccination. IFX is not yet covered by medical insurance, but according to relevant data, IFX is still expected to be an effective treatment [14].

Other biologics

Other reported biologics include TNF-AA receptor antagonist (Etanercept), anti-IL-6 receptor antibody (Tocilizumab) and IL-1 receptor antagonist (Anakinra). Etanercept is characterized by a short half-life and low side effects. In a double-blind, randomized, controlled trial using IVIG plus etanercept subcutaneously as first-line treatment, changes in coronary artery diameter were significantly lower in the IVIG group than in the IVIG+ etanercept group, although there was no significant difference in fever remission. Further use is under study.

Protease inhibitors

Ulinastatin (UTI)

UTI is a human urinary trypsin inhibitor, produced by many organs, including liver, kidney, pancreas, etc., to reduce damage to vascular endothelial cells by inhibiting the activity of proteolytic enzymes and inflammatory cytokines released by neutrophils [13]. Its use may be considered in combination with IVIG as a primary treatment or as an additional treatment for patients who do not respond to IVIG (class ii B, C). The optimal dose for pediatric patients has not yet been determined. Studies have shown that 3 to 6 times a day, not exceeding 300,000 units/day, at 5,000 U/kg, with a half-life of 40 minutes and an intravenous dose of 300,000 units /10 ml. The first documented combination of UTI and IVIG was designed to reduce the incidence of non-responders to IVIG and CAA. Patients with a history of drug allergy or urinary tract infection should take medication with caution [12].

Other Sivelestat sodium hydrate

Sivelestat Sodium Hydrate (SSH) is a more potent and selective inhibitor of neutrophil elastase and another protease inhibitor like UTI. SSH is used for the treatment of acute lung injury associated with SYS-TEMic inflammatory response syndrome and for KD. In some reports, SSH has been used in combination with IVIG for initial treatment or additional therapy in patients who do not respond to Ivig.109, 10. Although the optimal dose for pediatric patients has not been determined, several reports have shown continuous intravenous infusion of 0.2mg/kg/h in KD. There is no evidence of indication, dosage or prescription for administration.

Plasma Exchange (PE)

PE can correct hyper cellular schizophrenia through inflammatory cytokines and chemokines directly involved in the pathogenesis of KD. PE mainly in ivig-treated no responders, PE is a kind of invasive treatment, its side effects are mostly of low blood pressure/shock, bleeding, anemia, and associated with extracorporeal circulation in the low temperature, coagulation disorders associated with albumin replacement, allergic reactions, hypocalcemia, etc., the drug should be deep sedation, often need breathing machine or intensive care unit management, At the same time, calcium ions should be tested regularly and electrolytes (ii A,C) should be adjusted appropriately. PE has a long history, dating back to before IVIG. However, PE is often used as the last resort when other treatment schemes fail, and is limited to severe patients, and effective prospective clinical trials are lacking [12-13].

Antiplatelet drugs

Aspirin (ASA)

ASA inhibits cyclooxygenase, Thromboxane A2 (TXA2) and Prostaglandin E2 (PGE2). ASA acetylates the cyclooxygenase and prevents it from binding to the original substrate (arachidonic acid) to inhibit TXA2 production. All dosage forms of ASA are covered by Medicare, including the cardiovascular sequelae caused by KD. In the acute phase, moderate doses of ASA (30-50mg/kg/ day, three times a day) are recommended for anti-infection until fever abates, and the dosage should be reduced to 3-5mg/kg for 48-72 hours without recurrent fever, once a day. Continue to use for 2-3 months after the onset of KD. ASA should continue to be used in patients with CAA because of its important role in long-term antithrombotic therapy (class I, A). Mortality rates have improved since ASA was widely applied to KD in the 1970s. In recent years, it has been found that the inhibitory effect of CAA in the acute phase is highly specific to IVIG, that is, low dose ASA may be used from the early stage (class I, C). However, the possible complications of the drug include liver insufficiency, shock, allergic reactions, gastrointestinal ulcers, multiple nosebleeds and melena. When the above complications occur in children, the dose should be reduced or ASA should be discontinued. If KD is present in influenza or chickenpox patients, or in convalescence, IVIG alone or in combination with anti-infecting or anti-platelet agents other than ASA. Relevant reports still suggest that children taking low doses of ASA should be inoculated, and the relevant clinical symptoms should be strictly observed [12-15].

Other

Antiplatelet agents of different mechanisms include dipyridamole (inhibition of phosphodiesterase → increased cAMP concentration in platelets), ticlopidine and clopidogrel (both ADP receptor inhibitors→increased platelet adenylate cyclase activity→increased platelet cAMP concentration). Dipyridamole, given in 3 doses at a recommended dose of 2 to 5mg/kg/ day, can cause headaches and serious side effects including worsening angina. The recommended dose of ticlopidine is 2 -- 5mg/ kg/ day in 3 doses, but should be used with caution because of complications such as thrombotic thrombocytopenic purpura, granulocytopia, and severe liver injury. Clopidogrel, recommended dose 0.2-1mg/kg/ day, once daily, but with bleeding complications. Clopidogrel and ASA were used to prevent thrombosis, and the mechanism of action was similar to ticlopidine, but the liver damage was less (ii B, C). Some drugs are not covered by medical insurance, so attention should be paid to this practical problem in clinical use.

Other cardiovascular drugs

Anticoagulant

Warfarin

Warfarin plays an anticoagulant role by inhibiting the synthesis of coagulation factors II, VII, IX and X, which can prevent CAA thrombosis. 0.16 mg/kg/day for children younger than 12 months and 0.04 to 0.10 mg/kg/day for children older than 1 year and younger than 15 years, once daily (i, C). Because the utility in the same individual is variable, the dose should be adjusted periodically with PT-INR, with a recommended target level of 2.0 to 2.5. In the acute phase, warfarin has difficulty controlling the inflammatory response and takes time to promote remission and stabilization. It has been reported that warfarin may be safer after continuous intravenous heparin administration if immediate anticoagulation is required in the acute phase of KD. In general, patients without CAA do not need anticoagulants. Combination of ASA and warfarin in patients with large CAA has been reported in a retrospective study to prevent long-term heart disease. Warfarin is not recommended for small aneurysms, but can be considered for moderate aneurysms depending on the status of the aneurysm. The biggest side effects are bleeding, such as nasal and gum bleeding, intracranial and abdominal bleeding [12-15].

Heparin

If CAA complications and early thrombosis are present, switch to oral warfarin from continuous intravenous heparin until inflammation subside. Some reports suggest that heparin is safer than warfarin in the first place. It is suitable for large CAA, myocardial infarction and thrombosis in CAA. It is mainly divided into ordinary heparin and low molecular weight heparin. The dosage of ordinary heparin also varies. Ordinary heparin: 10 to 20 units /kg/h continuous infusion (50 units /kg for the first time); Low molecular weight heparin: no pediatric dose has been established. Physicians should monitor Heparin-Induced Thrombocytopenia (HIT), bleeding, liver insufficiency, hair loss, rash, and diarrhea when using drugs [11-12]. Patients with moderate or large CAA who were initially treated with warfarin were more likely to experience severe bleeding than those who were initially treated with heparin and then switched to warfarin. Low molecular weight heparin has less HIT and bleeding than ordinary heparin (ii A, C).

Direct oral anticoagulant (DOAC)

Direct inhibition of thrombin and coagulation factor Xa plays an anticoagulant role in preventing atrial fibrillation thrombosis and venous thrombosis. In adults, it is used to prevent hemorrhagic stroke and systemic embolic nonvalvular atrial fibrillation in stroke patients, and to treat and prevent recurrent deep vein thrombosis and pulmonary embolism. Adult doses were 150mg dabigatran twice daily, rivaroxaban 15mg once daily, apixaban 5mg twice daily, and edoxaban 60mg once daily (30mg if patients weighed less than 60kg). Doses for children have not been determined. At present, KD treatment is not covered by medical insurance. In the future, it could be an alternative to warfarin and heparin.

Thrombolytic Drugs

Myocardial infarction often occurs within 2 years after the onset of KD, and acute coronary artery obstruction is mainly caused by intra-aneurysmal thrombosis. The Japan Cardiology Society guidelines suggest that thrombolytic therapy is better for children because they are smaller and have fewer bleeding complications. In adults, thrombolysis is recommended if PCI cannot be performed within 12 hours of onset and if the patient is first exposed within 2 hours. Asymptomatic thrombosis may also be thrombolytic when CAA and myocardial infarction are threatening. Thrombolytic drugs are divided into urokinase, alteplase and monteplase. The dosage of different drugs is very different. Urokinase is injected intravenously for 10,000 to 16,000 units/kg (up to 960,000 units), and the infusion time is 30 to 60 minutes. Intra coronary: 400,000 units per kg over 10 minutes. Four times at most. Alteplase is given intravenously in the range of 290,000 to 435000 units /kg at 10% of the total dose for 1 to 2 minutes with the remainder completed within 1 hour. Monteplase was given intravenously at 27,500 units /kg for 2 to 3 minutes. After the use of drugs, cerebral hemorrhage, hemorrhagic cerebral infarction, gastrointestinal hemorrhage, pulmonary hemorrhage, allergic reaction, shock and other complications may occur [8-13].

Antiangina drugs and coronary artery dilators

Beta blockers

β-blockers are the drugs of choice for angina pectoris, and there are different types of common drugs. For example, propranolol is the only insurance drug for children with coronary artery stenosis accompanied by myocardial ischemia, heart failure and arrhythmia (but not angina pectoris) after myocardial infarction. The use of carvedilol in children has the potential to cause heart failure, starting at low doses and personal maintenance doses based on tolerability and therapeutic benefit.

Calcium antagonists

It can inhibit calcium ion cells in vascular smooth muscle cells and prevent coronary artery spasm, making it a first-line treatment for angina pectoris of coronary heart disease. Amlodipine is covered as an insurance drug for the treatment of hypertension in children 6 years and older, while nifedipine and diltiazem are not prescribed for children.

Nitrate

Nitrate increases coronary blood flow due to coronary artery dilation and reduced preload, as well as reduced preload and afterload of the left ventricle, thereby improving myocardial ischemia. As long-term endurance increases, aimless use should be avoided. Sublingual nitroglycerin tablets (1-2 tablets for adults, 0.3-0.6 mg, 1/2 to 1/3 tablet for children, depending on body size) and continuous intravenous fluids (0.1-20μg/kg/min).

Reference

1. Jiao Fuyong, Jindal Ankur Kumar, Pandiarajan Vignesh, Khubchandani Raju, Kamath Nutan (2017) The emergence of Kawasaki disease in India and China. Global cardiology science & practice 11(3). e201721
2. Soni Priya R and Noval Rivas Magali and Arditi Moshe (2020) A Comprehensive Update on Kawasaki Disease Vasculitis and Myocarditis. Current rheumatology

reports 22(2): 6.

3. Lo Mindy S,Newburger Jane W (2018) Role of intravenous immunoglobulin in the treatment of Kawasaki disease. International journal of rheumatic diseases 21(1). :64-69.
4. McCrindle Brian W (2017) Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation 135(17): e927-e999.
5. Esposito Susanna, Bianchini Sonia, Dellepiane Rosa Maria, Principi Nicola (2016) Vaccines and Kawasaki disease. Expert review of vaccines 15(3).
6. Muzhl, JFY, Xie KSH (2001) Interpretation of guidelines for diagnosis and management of cardiovascular sequelae of Kawasaki disease (JCS/JSCS 2020). Chinese Journal of Contemporary Pediatrics 23(03): 213-220.
7. Dionne Audrey, Dahdah Nagib, Singh Grewal Davinder, Burgner David P, Newburger Jane W (2020) Anti-thrombosis management of patients with Kawasaki disease: Results from an international survey. International journal of cardiology 12(9): 154-158.
8. Newburger Jane W (2017) Kawasaki disease: Medical therapies. Congenital heart disease 12(5).
9. Fuyong Jiao, Zhilong Mu, Xian Wang (2016) Update on Study of Kawasaki Disease. Journal of Pediatric and Womens Healthcare 10(7).
10. Fu-Yong JiaoXiaohua YanXiao fang Wu (2016) The xi'an Experience of Kawasaki Disease-Lessons Learnt over 5 years. Indian Pediatrics 11(5).
11. Surjit Singh, Avinash Sharma, Fu-Yong Jia (2016) Kawasaki Disease: Issues in DiagnosisAnd Treatment-A Developing Country Perspective. Indian Pediatric 13(4): 140-145.
12. Jiao Fuyong, Yan Xiaohua, Lin Jing (2012) New progress in the treatment of Kawasaki disease. Chinese Medical Science 10(7).
13. Fu Yong Jiao, Yuxian Zhang, Jing Lin (2011) A Clinical Study of Kawasaki Disease in 225 Chinese Children. Malaysian Journal of Paediatrics and Child Health 9(3).
14. Fu Yong Jiao, L Yang A, Y LiA (2001) Epidemiologic aspects of Kawasaki Disease in four Chinese provinces. Journal of Tropical Pediatric 9(7).
15. Fuyong Jiao, Yue-hua Li, Takenuchi Tomitsu (1998) Epidemiological characteristics of Kawasaki disease in different regions of the world. Chinese Journal of Epidemiology 11(5).