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Guideline

Guidelines for medical treatment of acute Kawasaki disease: Report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version)

Research Committee of the Japanese Society of Pediatric Cardiology and
Cardiac Surgery Committee for Development of Guidelines for Medical Treatment of Acute Kawasaki Disease

The primary purpose of practical guidelines is to contribute to timely and appropriate diagnosis and treatment of a given disease or condition, in addition to providing current medical information on pathogenesis and treatment, as determined by specialists in the field. Guidelines, however, should not be considered procedure manuals that limit the treatment options of practitioners, because treatment modalities other than those recommended in such guidelines are often required. Such treatment choices are the result of comprehensive analysis of all medical circumstances, including patient condition, treatment option, and disease severity. Furthermore, certain drugs shown to be useful in studies conducted in other countries may not yet have been approved for use here in Japan. The results of clinical research (including randomized controlled trials) must be verified in subsequent research, and the safety and effectiveness of a particular treatment may take several months to confirm.

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Evidence classification

Recent clinical guidelines typically provide evidence levels based on study design and reported effectiveness.

Level (class) based on study design

These are defined as follows: class Ia, systematic reviews, meta-analyses; class Ib, randomized controlled trials; class IIa, non-randomized controlled trials; class IIb, other quasi-experimental studies; class III, non-experimental reports (comparative studies, correlation studies, case studies); and class IV, opinions of committees of experts and authorities.

Classification (grade) based on efficacy

These are given as follows: grade A, highly recommended; grade B, recommended; grade C, recommended, but evidence is uncertain; and grade D, contraindicated.

The present guidelines will use these classification systems in reviewing the available evidence for the various treatments.

Background of the present revision of the treatment guidelines

In July 2003, the Scientific Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery published its *Treatment Guidelines for Acute Kawasaki Disease* (KD). These guidelines were designed to present, in a clinically relevant manner, the findings of Ministry of Health research done from 1998 through 2000 by the Onishi group at Kagawa Medical University (working under the official title, "The Pediatric Pharmaceutical Investigation Research Group"). This research had been published as "Research designed to identify and solve problems in the suitable use of pharmaceuticals for pediatric medical treatment: pharmaceuticals in cardiology" and had originally been conducted to provide clinical data for the approval of single-use i.v. immunoglobulin (IVIG).

During the 9 years that have passed since the publication of the previous guideline, new data have been collected, and reports on new drug treatments have been published. Members of the International Kawasaki disease Symposium have been waiting

for a revision of the previous Japanese guideline. Thus, the Scientific Committee was restructured and assigned the task of revising the guideline.

Purpose and methods

Data on IVIG that have accumulated since it was approved and first marketed have confirmed the efficacy and safety of single-use IVIG therapy. In addition, the incidence of coronary artery lesions (CAL) has gradually decreased every year since IVIG treatment was introduced in Japan.[1] The incidence of giant coronary artery aneurysms (CAA), however, has remained almost unchanged, which highlights the importance of timely use of second- and third-line treatments for IVIG-resistant patients.

In developing the present guideline, we carefully reviewed the most recent available literature, classified evidence and efficacy, and revised suggested treatment methods, including procedures for selecting first-, second- and third-line medications, with a special focus on off-label uses. For example, the previous guideline did not mention new therapeutic agents such as infliximab (IFX), cyclosporin A (CsA), or methotrexate (MTX). In the present edition, risk/benefit considerations are also clearly presented, based on data collected in and outside Japan. Despite the publication of almost 200 reports every year on KD, there is still no universally accepted treatment for IVIG resistance. This is also the case, however, for many other disorders, such as autoimmune disease and rheumatoid conditions, given that no single medication will benefit all patients in the same way. Thus, to ensure optimal outcome, physicians must treat each patient individually.

Diagnosis and treatment of incomplete KD

In the published results of the 21st Nationwide Survey of KD by Jichi Medical School a total of 23 730 cases of KD were reported in Japan during the 2 year period 2009–2010.[1] Diagnosis of KD follows the criteria outlined in the fifth edition of the diagnosis guidelines for KD,[2] which requires that at least five of the following six principal symptoms are present: (i) fever persisting ≥5 days (including fever that subsides before the fifth day in response to therapy); (ii) bilateral conjunctival congestion; (iii) changes in lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa; (iv) polymorphous exanthema; (v) changes in peripheral extremities: reddening of palms and soles, indurative edema (initial stage); membranous desquamation from fingertips (convalescent stage); and (vi) acute non-purulent cervical lymphadenopathy.

Kawasaki disease, however, may also be diagnosed when only four of the aforementioned symptoms are present, if during the period of illness either 2-D echocardiography or coronary angiography shows CAA, including dilation of coronary artery, and other causes of CAA can be excluded. A diagnosis of KD is possible even if five or more of the principal symptoms are not present, if other conditions can be excluded and KD is suspected – a condition known as incomplete KD. Indeed, approximately 15–20% of KD patients have incomplete KD. But, even if a patient has four or fewer of the principal symptoms, the illness should not be regarded as less severe, because cardiovascular abnormalities are not rare in patients with incomplete KD. For this reason, even patients with fewer than five of the aforementioned symptoms should be evaluated for KD. Early treatment is essential, particularly when fever is present, because CAL development in such cases is not uncommon. Diagnosis of incomplete KD is not a simple matter of adding up the number of overt KD symptoms: the importance and individual characteristics of each symptom of the illness must be correctly assessed. For example, redness and crusting at a bacille Calmette–Guérin (BCG) inoculation site in infants younger than 1 year and multilocular cervical lymphadenopathy in children aged ≥4 years are characteristic features of KD.

Basic pathology

The 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides defines KD as an arteritis associated with mucocutaneous lymph node syndrome, predominantly affecting medium and small arteries.[3] There is very little damage to veins. The location of pathological changes clearly differentiates KD from other vasculitis syndromes, given that the principal danger of KD is inflammatory vasculitis of the coronary arteries. Edematous lesions develop in the intima media, and vascular fragility increases due to partial rupture of the internal and external elastic lamina. As a result, the arterial wall can no longer withstand its internal pressure, particularly diastolic pressure, and becomes distended and deformed, leading in severe cases to aneurysm formation. Only a few other diseases cause distension of coronary arteries. These include vasculitis resulting from Epstein–Barr virus infection, lupus, classical periarteritis nodosa, and atherosclerotic lesions. Calcification can also occur in rare cases and affect coronary arteries, for example in cases of renal dialysis in adults and herpes infection in newborns.

Patients with KD may develop multiple lesions in the proximal region and vessels branching out from it. As aneurysms begin to calcify, further pathological distension or development of aneurysms and intimal thickening may develop 2–3 years later in areas with previously disrupted internal and external elastic lamina.[4]

Coronary artery lesions

The principal characteristics of KD are dilation of coronary arteries and CAA. Most CAA occur in the proximal region and its branches, and arteries with a CAA measuring ≥8 mm in diameter are very unlikely to regain their normal morphology. Right CAA may lead to occlusion or recanalization, and left CAA may progress to stenotic lesions.

Rupture of the internal elastic lamina in the intima media of the dilated area weakens the artery wall, and coronary arterial pressure then becomes the direct mechanical cause of distension. In rare cases, aneurysms may develop in branches of the axillary or celiac arteries. During acute KD, vasculitis worsens during the first 7 days after disease onset. In patients with mild illness, the vasculature returns to normal by the second or third week.

Suitable pharmaceuticals for treating KD

Treatment of acute KD

The principal objective in treating acute KD is minimizing the risk of developing CAL. In practice, this means quickly suppressing the acute-phase inflammatory reaction caused by KD. Except in cases of very mild KD, IVIG should be started before illness day 7. Histological studies have shown that arteritis typically develops by 8 or 9 days after KD onset. Therefore, treatment should begin before this point, to suppress arteritis and hasten resolution of fever and normalization of inflammation markers. In patients with incomplete KD, IVIG should also be begun as soon as possible after a diagnosis of KD, especially if fever is present. In approximately 80% of cases, fever should be lowered to ≤37.5°C within 48 h of starting IVIG. In 40% of IVIG-resistant patients, fever can be reduced to ≤37.5°C with additional IVIG of 1 g/kg. Persistent fever after 48 h of starting IVIG should be regarded as evidence of IVIG-resistant KD. Prevention of CAA in such patients may largely depend on the selection of subsequent treatment.

In addition to CAL, other cardiovascular complications may develop in patients with acute KD, including myocarditis, pericardial effusion, valvular regurgitation, and, rarely, arrhythmia. Specific treatment may be required for these sequelae, as well as for cardiac dysfunction or heart failure. Furthermore, other symptom-specific treatment may be required for systemic complications such as edema, hypoalbuminemia, electrolyte imbalances (i.e. hyponatremia), paralytic ileus, hepatic dysfunction, cholecystitis, impaired consciousness, convulsions, anemia, diarrhea, vomiting, and dehydration. Particularly during high-dose IVIG infusion, care must be taken to prevent volume overload so as to protect the patient from complications such as heart failure.

There is currently no universally accepted classification system to evaluate KD severity and need for IVIG use, although many such scoring systems have been proposed. Initial attempts were made by Asai and Kusakawa,[5] which were followed by the Iwasa score[6] and Harada score.[7] More recently, predictive models designed to evaluate the possibility of IVIG resistance were proposed, including the Kobayashi score,[8] Egami score,[9] and Sano score.[10] In general, such predictive models consider factors such as age, gender, days of illness, white blood cell count, %neutrophils, hematocrit, platelet count, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, sodium, and albumin. Recently, a randomized controlled trial found that IVIG plus steroid as initial therapy for patients predicted to be at high risk for IVIG resistance improved clinical and coronary arterial outcomes.[11–13] The effectiveness of such predictive models, however, has not been confirmed in large-scale prospective cohort studies or meta-analyses, and controversy remains as to whether initial therapy with IVIG plus steroids is the optimal treatment.

Choice of treatment for IVIG-resistant patients

Several second-line treatment options are available if fever persists or has reappeared at 24 h after first-line treatment. The efficacy of these second-line treatments for resistance to first-line treatment is currently being investigated by researchers in many countries, but evidence remains limited due to the lack of randomized controlled trials.

Options for second-line treatment include additional IVIG, i.v. methylprednisolone pulse (IVMP), prednisolone (PSL), IFX, ulinastatin (UTI), CsA, MTX, and plasma exchange (PE). The decision to use any of these treatments requires careful consideration of patient characteristics. At present, the most commonly used second-line treatment is additional IVIG,[1] which is sometimes given in combination with other medications. As for steroids, a retrospective study noted a high incidence of giant aneurysms.[14] That small uncontrolled case study reported that several patients had received steroids before rupture of coronary arteries, which suggests that physicians should carefully consider the decision to use steroids for patients with KD if CAA are already present. When steroids, biologics, or immunosuppressants are given to infants, there is also a risk of long-term side-effects, and questions remain regarding the general safety of such medications. Thus, a careful risk/benefit evaluation should be done to consider the likelihood of such adverse effects versus the possibility of CAA formation.

Algorithm for selecting optimal treatment

To decrease the risks of first-line IVIG resistance and CAA, it seems reasonable to consider risk stratification using predictive models and to select more-aggressive initial treatment for patients at high risk of IVIG resistance. Such patients should be treated with 2 g/kg of IVIG in combination with either 2 mg/kg per day PSL or 30 mg/kg per day IVMP. If the patients fail to respond to these treatments, a third-line treatment will be upgraded to a second-line treatment.

Because few studies have assessed the efficacy of medications other than IVIG retreatment, it is impossible at this time to assign an objective order of these treatment options. The present guidelines, however, offer evidence levels and grades to assist physicians in selecting appropriate alternatives. Various methods of calculating KD patient risk scores and, thereby, estimating KD severity have been developed at a number of institutions by different physicians, based on their particular experience with KD.[8–10] The Japanese Society of Pediatric Cardiology and Cardiac Surgery does not intend to limit the treatment options available to clinicians, especially when such options have already received ethics committee approval at their institution. Instead, the judgment of physicians in selecting treatments should be respected, for practical reasons as well. Such treatments may be given after a physician has established a sufficient basis for selecting a given treatment and received informed consent/assent from the family/patient (Fig. 1).

Immunoglobulin

Purpose

Currently, the most effective anti-inflammatory treatment for KD is early IVIG.[15–17] The latest systematic review by the Cochrane Collaboration states that CAL development can be reduced by a single dose of 2 g/kg IVIG given before the 10th day after onset.[18]

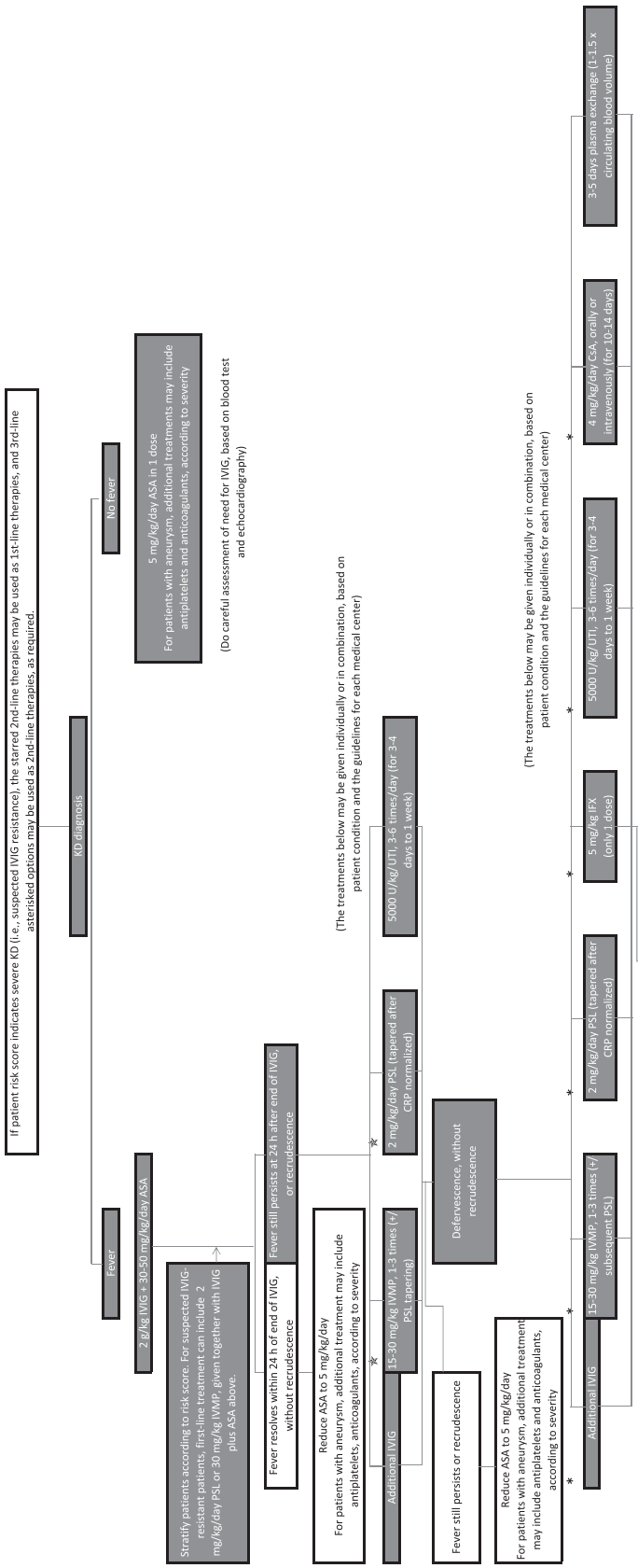

Fig. 1 Algorithm for the treatment of acute Kawasaki disease (KD). ASA, acetyl salicylic acid; CRP, C-reactive protein; IFX, infliximab; IVIG, i.v. immunoglobulin; IVMP, i.v. methylprednisolone pulse; PSL, prednisolone; UTI, ulinastatin.

Mechanism of action

Because the causes of KD are unknown, the mechanisms underlying the therapeutic benefits of IVIG remain speculative. Table 1 lists the hypothesized mechanisms of action.[19–22]

Indications

I.v. immunoglobulin is suitable for almost all cases of typical acute KD, that is, when KD is diagnosed based on the presence of the principal symptoms specified in the criteria of the diagnostic guideline for KD[2] and the patient is at risk for CAL. For patients with symptoms that only partially fulfill the diagnostic criteria, incomplete KD may be diagnosed – if other diseases or conditions can be excluded – after which IVIG should be started as quickly as possible due to the risk of CAL.[17]

In cases of less severe KD or spontaneous defervescence, clinicians may refrain from IVIG, in accordance with the considerations detailed in the Ministry of Health Group Committee guidelines for IVIG (Harada score)[7] and disease severity standards established at the physician's institution.

Data from the 21st Nationwide Survey of KD show that IVIG was given to 89.5% of patients.[1]

Table 1 Immunoregulatory effects of IVIG[19–22]

I.	Fc receptor-mediated effects
	Blockade of Fc receptors on macrophages and effector cells
	Antibody-dependent cellular cytotoxicity
	Induction of inhibitory FcγRIIB receptors
	Promotes clearance of antibodies that block FcRn
II.	Anti-inflammatory effects
	Attenuation of complement-mediated damage
	Decrease in immune complex-mediated inflammation
	Induction of anti-inflammatory cytokines
	Inhibition of activation of endothelial cells
	Neutralization of microbial toxins
	Reduction in steroid requirements
	Modulation of matrix metalloproteinases
III.	Effect on B cells and antibodies
	Control of emergent bone marrow B-cell repertoires
	Negative signaling through Fcγ receptor
	Selective downregulation/upregulation of antibody production
	Neutralization of circulating autoantibodies by anti-idiotypes
IV.	Effect on T cells
	Regulation of T-helper cell cytokine production
	Neutralization of T-cell superantigens
	Regulation of apoptosis
V.	Effect on dendritic cells
	Inhibition of differentiation and maturation
	Regulation of inflammatory cytokine production
VI.	Other
	Mutually interacts with immunological molecules
	Suppression of autoantibody production against vascular endothelial cells
	Acceleration of phagocytosis arising from binding of neutrophils and macrophages (opsonin effect)
	Suppression of inflammation-related gene S100 mRNA
	Suppression of MCP-1 receptor CCR2 gene expression produced by macrophages

CCR2, C-C chemokine receptor type 2; FcγRIIB, Fc gamma receptor IIB; FcRn, neonatal Fc receptor; IVIG, i.v. immunoglobulin; MCP-1, monocyte chemotactic protein-1.

Treatment method and dosage

Period of treatment

I.v. immunoglobulin should be started on or before the seventh day after KD onset. It is essential to quickly reduce inflammation and duration of fever, definitely before illness day 8 or 9, when CAL begin to appear. Markers of systemic inflammation, for example CRP and neutrophil count, should be lowered as well.

One study compared patients receiving IVIG on the fifth of illness day or earlier with those who received IVIG on the sixth through ninth days of illness. Although duration from treatment onset to defervescence was slightly longer overall among those receiving IVIG earlier, total duration of fever was shorter. Moreover, the groups did not differ in incidence of fever recurrence or additional IVIG treatment, or in number of days of hospitalization. Furthermore, 1 year after appearance of symptoms, those who had received IVIG earlier had a lower incidence of CAL.[23]

Dosage

The suggested IVIG dosage for acute KD is 2 g/kg per day (single use), 1 g/kg per day for 1 or 2 days continuously (modified single use), or 200–400 mg/kg per day, over 3–5 days (divided dosing).

Studies in a number of countries have shown that, as compared with divided-dose regimens, a single dose of 2 g/kg per day significantly reduced CAL incidence, more quickly normalized inflammation markers, and was more effective in reducing fever.[4,5] As for 1 g/kg/day use, if clinical efficacy is seen on the first day, it might not be necessary to continue treatment into the second day.

The 21st Nationwide Survey of KD found that a single dose of 2 g/kg per day IVIG was used in 85% of reported cases and that 1 g/kg per day was given for 1 or 2 days in 6.2% and in 7.7% of cases, respectively.[1]

There is no consensus in Japan as to whether older/larger children should be treated with 2 g/kg IVIG or a lower dose.

As for 2 g/kg regimen, the treatment rate varies slightly for different products, although IVIG is typically given over a period of approximately 12 h in North America. In Japan, one product permits use within a similar 12 h period, but the total volume of 2 g/kg IVIG is usually given over a period of 24 h. Because volume overload might occur when the treatment rate is too fast, which can lead to cardiac dysfunction, it is important to adhere to the recommended treatment rate and carefully observe patient hemodynamics.

Product types and directions for use

At present, four brands of IVIG are approved for KD in Japan (Table 2): two are processed with polyethylene glycol (PEG), one is sulfonated, and one is processed to ensure a pH of 4 (acidic). No major differences in efficacy have been reported. Table 2 lists the characteristics of these products, as described in their respective product inserts.

The principal differences are as follows.

Table 2 IVIG medications

Product name	Kenketsu Venilon-I (for i.v. use)	Kenketu Glovenin-I (for i.v. use)	Kenketu Venoglobulin IH (for i.v. use)	Nisseki Polyglobin N (for i.v. use)
Generic name	Freeze-dried sulfonated human normal immunoglobulin	Freeze-dried polyethylene glycol-treated human normal immunoglobulin	Polyethylene glycol-treated human normal immunoglobulin	pH 4-treated acidic human normal immunoglobulin
Company (manufacturer/distributor)	Kaketsuken-Teijin Pharma Limited	Nihon Pharmaceutical–Takeda Pharmaceutical	Japan Blood Products Organization-Mitsubishi Tanabe Pharma	Japan Blood Products Organization-Japan Red Cross Society
Form of medication	Freeze-dried preparation	Freeze-dried preparation	Liquid medication	Liquid medication
Constituents (in 2.5 g of product)	Sulfonated human immunoglobulin G 2500 mg Glycin 1125 mg Human plasma albumin 125 mg D-mannitol 500 mg Sodium chloride 450 mg	Polyethylene glycol treated human immunoglobulin G 2500 mg 750 mg D-mannitol 225 mg Glycin 450 mg Sodium chloride	Human immunoglobulin G 2500 mg D-sorbitol 2500 mg Sodium hydroxide Suitable amount Hydrochloric acid Suitable amount	Human immunoglobulin G 2500 mg Maltose hydrate 5000 mg Hydrochloric acid Suitable amount Sodium hydroxide Suitable amount
Treatment route and dosing	Normally given as sulfonated human immunoglobulin G either i.v. or by direct i.v. infusion, at 200 mg (4 mL)/kg bodyweight/day over a 5 day period. Alternatively, a single dose of 2000 mg (40 mL)/kg bodyweight may be given i.v. In addition, in the case of 5 day treatment, this period may be adjusted according to patient age and condition. In the case of 1-time i.v., the dose may be similarly reduced as required.	Normally given as human immunoglobulin G either i.v. or by direct i.v. infusion, at 200 mg (4 mL)/kg bodyweight/day over a 5 day period. Alternatively, a single dose of 2000 mg (40 mL)/kg bodyweight may be given i.v. In addition, in the case of 5 day treatment, this period may be adjusted according to patient age and condition. In the case of 1-time i.v. treatment, the dose may be similarly reduced as required.	Normally given as human immunoglobulin G either i.v. or by direct i.v. infusion, at 400 mg (8 mL)/kg bodyweight/day over a 5 day period. Alternatively, a single dose of 2000 mg (40 mL)/kg bodyweight may be given i.v. The dose may be reduced according to patient age and condition.	Normally given as human immunoglobulin G either i.v. or by direct i.v. infusion, at 200 mg (4 mL)/kg bodyweight/day, over a 5 day period. Alternatively, a single dose of 2000 mg (40 mL)/kg bodyweight may be given i.v. In addition, in the case of 5 day treatment, this period may be adjusted according to patient age and condition. In the case of 1-time i.v. treatment, the dose may be similarly reduced as required.
	A sudden drop in blood pressure may result if the medication is given too rapidly (special care is required when the patient's blood contains little or no endogenous γ-globulin).			
Points to consider in treatment and dosing	Treatment speed: 1) On the first day, the first 30 min should be at a rate of 0.01–0.02 mL/kg/min. If no side-effects or other abnormalities are observed, treatment speed may gradually be increased to 0.03–0.06 mL/kg/min. From the second day onward, the patient may be started at the highest rate tolerated on the previous day. 2) In cases of 1-time treatment of 2000 mg (40 mL)/kg to KD patients, treatment rates in 1) above should basically be adhered to, and the i.v. infusion should given over a period of at least 12 h.	Treatment speed: As there is the possibility of shock or other serious side-effects during the first hour of treatment on the first day, and also when treatment speed is increased, the patient must be carefully monitored during these times. 1) On the first day, the treatment speed should be 0.01 mL/kg/min during the first hour. When the absence of side-effects and other problems has been confirmed, the speed may be gradually increased. However, it should not exceed 0.03 mL/kg/min. On the second day and later, treatment may be started at the highest rate tolerated on the previous day. 2) In the cases of 1-time treatment of 2000 mg (40 mL)/kg i.v. to KD patients, the rates in 1) should basically be adhered to, with careful attention to sudden increases in circulatory blood volume. The i.v. should be given over a period of at least 20 h.	Treatment speed: As there is a possibility of shock or other serious side-effects during the first hour of treatment on the first day, and also when treatment speed is increased, the patient must be carefully monitored during these times. 1) On the first day, the treatment speed should be 0.01 mL/kg/min during the first hour. When the absence of side-effects and other problems has been confirmed, the rate may gradually be increased. However, it should not exceed 0.03 mL/kg/min. On the second day and thereafter, treatment may be started at the highest rate tolerated on the previous day. 2) In the case of 1-time treatment of 2000 mg (40 mL)/kg i.v. to KD patients, the rates in 1) should basically be adhered to, with careful attention to sudden increases in circulating blood volume. The i.v. should be given over a period of at least 20 h.	Treatment speed: 1) On the first day, the drug should be delivered at a rate of 0.01–0.02 mL/kg/min during the first 30 min. If no side-effects or other abnormalities are observed, the rate may gradually be increased to 0.03–0.06 mL/kg/min. From the second day onward, the patient may be started at the highest speed tolerated on the previous day. 2) In the case of 1-time treatment of 2000 mg (40 mL)/kg to KD patients, the treatment rates in 1) above should basically be adhered to. The i.v. should be given over a period of at least 12 h.
Contraindications	Patients with a history of shock after receiving any component of this medication.	Patients with a history of shock after receiving any of the components of this medication	Patients with a history of shock after receiving any of the components of this medication; patients with inherited glucose intolerance	Patients with a history of shock after receiving any of the components of this medication
Important fundamental points	For KD patients who do not satisfactorily respond to initial IVIG treatment (e.g. patients with persistent fever) and whose symptoms do not improve, additional IVIG should only be given when judged necessary (the data do not conclusively demonstrate the efficacy and safety of additional doses of this drug).	For KD patients who do not satisfactorily respond to initial IVIG treatment (e.g. patients with persistent fever) and whose symptoms do not improve, additional IVIG should only be given when judged necessary (the data do not conclusively demonstrate the efficacy and safety of additional doses of this drug).	For KD patients who do not satisfactorily respond to initial IVIG (e.g. patients with persistent fever) and whose symptoms do not improve, additional IVIG should only be given when judged necessary (the data do not conclusively demonstrate the efficacy and safety of additional doses of this drug). The incidence of liver dysfunction, including elevated AST and ALT, is high when this preparation is given to KD patients, especially to infants younger than 1 year. Patients should be closely monitored after treatment.	For KD patients who do not satisfactorily respond to initial IVIG treatment (e.g. patients with persistent fever) and whose symptoms do not improve, additional IVIG should only be given when judged necessary (the data do not conclusively demonstrate the efficacy and safety of additional doses of this drug).
Side-effects All patients	1.24% (165/13,339)	8.8% (79/893)	11.46% (285/2486)	5.11% (269/5260)
Side-effects Acute KD	1.08% (15/1389)	5.6% (9/160)	NA	8.30% (95/1144)

Incidence of side-effects reported in KD patients		1.14% (12/1053 patients), but incidence of severe side-effects was 0% (0 events in 0 cases), including shock in 0% (0 events in 0 patient), symptoms of suspected shock (e.g. cyanosis, hypotension) in 0.28% (4 events in 3 patients)	6.62% (48/725 patients), with severe side-effects occurring in 1.93% (30 events in 14 patients), including shock in 0.14% (1 event in 1 patient), symptoms of suspected shock (e.g. cyanosis, hypotension) in 2.07% (21 events in 15 patients)	10.96% (224/2044 patients), with severe side-effects in 2.89% (84 events in 59 patients), including shock in 0.78% (18 events in 16 patients) and symptoms of suspected shock (e.g. cyanosis, hypotension) in 2.74% (67 events in 56 patients)	8.97% (78/870 patients); severe side-effects in 1.15% (11 events in 10 patients), including shock 0% (0 events in 0 patients) and symptoms of suspected shock (e.g. cyanosis, hypotension) in 0.23% (2 events in 2 patients)
Severe side-effects		Shock, anaphylactic symptoms (<0.1%) Hepatic dysfunction, jaundice (incidence unknown) Aseptic meningitis (incidence unknown) Acute renal failure (incidence unknown) Thrombocytopenia (incidence unknown) Pulmonary edema (incidence unknown) Thromboembolism (incidence unknown) Heart failure (incidence unknown)	Shock, anaphylactic symptoms (0.1% to <5%) Hepatic dysfunction, jaundice (incidence unknown) Aseptic meningitis (incidence unknown) Acute renal failure (incidence unknown) Thrombocytopenia (incidence unknown) Pulmonary edema (incidence unknown) Thromboembolism (incidence unknown) Heart failure (incidence unknown)	Shock, anaphylactic symptoms (0.1 to <5%) Hepatic dysfunction (0.1 to <5%), jaundice (incidence unknown) Aseptic meningitis (0.1 to <5%) Acute renal failure (incidence unknown) Thrombocytopenia (incidence unknown) Pulmonary edema (incidence unknown) Thromboembolism (incidence unknown) Heart failure (incidence unknown)	Shock, anaphylactic symptoms (0.1 to <5%) Hepatic dysfunction, jaundice (0.1 to <5%) Aseptic meningitis (incidence unknown) Acute renal failure (incidence unknown) Thrombocytopenia (incidence unknown) Thromboembolism (incidence unknown) Heart failure (incidence unknown)
Severe side-effects	Allergic reactions	Rash (0.1% to <5%), sensation of heat, urticaria, pruritus, localized edema etc. (<0.1%), redness, swelling, blistering, dyshidrosis	Rash, urticaria, pruritus, blistering, pompholyx (0.1 to <5%), facial flushing, localized edema, generalized redness, purpuric rash, eczema, papule (<0.1%)	Rash, urticaria (0.1 to <5%), facial flushing, localized edema (<0.1%), pruritus, general erythema (incidence unknown) etc.	Fever, rash (0.1 to <5%), pruritus (<0.1%)
	Psychological/neurological		Seizure, trembling (0.1 to <5%), dizziness, numbness (less than 0.1%), impaired consciousness (incidence unknown)	Trembling, convulsions (0.1 to <5%), drowsiness (<0.1%), impaired consciousness, discomfort (incidence unknown)	
	Circulatory system	Reduced blood pressure, increased blood pressure (incidences unknown)	Abnormal facial color, cold extremities, chest tightness (0.1 to <5%), increased blood pressure, palpitations (incidence unknown)	Abnormal facial color, cold extremities (0.1 to <5%), elevated blood pressure, bradycardia (<0.1%)	
	Liver	Elevated AST, ALT etc. (0.1% to <5%)	Elevated AST, ALT, and ALP (0.1 to <5%)	Abnormal results on hepatic function tests: elevated AST, ALT, γ-GTP, ALP etc. (≥5%)	
	Respiratory system		Asthma symptoms, coughing (incidence unknown)	Coughing (<0.1%), asthma symptoms, hypoxemia (incidence unknown)	
	Digestive organs	Nausea, vomiting, loss of appetite, abdominal pain (<0.1%)	Nausea, vomiting (0.1 to <5%), diarrhea (<0.1%), abdominal pain (incidence unknown)	Nausea, vomiting, diarrhea (0.1 to <5%), abdominal pain (<0.1%)	
	Blood	Leukopenia, neutropenia, eosinophilia, hemolytic anemia, anemia (incidence unknown)	Eosinophilia, neutropenia, hemolytic anemia (<0.1%)	Neutropenia (<0.1%), leukopenia, eosinophilia, hemolytic anemia (incidence unknown)	Neutropenia, eosinophilia (0.1 to <5%), hemolytic anemia (<0.1%)
	Other	Headache, fever, chills, shivering (0.1% to <5%), fatigue (<0.1%), chest pain, reduced body temperature, increased CK (CPK), asthmatic symptoms (incidence unknown)	Headache, fever, coldness, shivering, angiodynia (0.1 to <5%), fatigue (<0.1%), arthralgia, myalgia, back pain, increased CK (CPK), hot flushes, moodiness, conjunctival hyperemia, hypothermia (incidence unknown)	Headache, fever, coldness, shivering, hypothermia (0.1 to <5%), melalgia (<0.1%) fatigue, arthralgia, back pain, increased CK (CPK), hot flashes, moodiness (incidence unknown)	Headache, nausea (0.1 to <5%)
Notes on suitability for treatment		Avoid co-treatment with other medications. Do not use any preparation that is not completely dissolved. Once dissolved, the medication should be used as soon as possible. Any liquid remaining after treatment should not be reused, due to the possibility of bacterial contamination.	Avoid co-treatment with other medications except pH-neutral infusions and fluid replacement solutions such as 5% glucose solution or biological saline solution.	Avoid co-treatment with other medications. Do not use product if it appears incompletely dissolved or there is excessive turbidity. Administer only after returning to room temperature. Any liquid remaining after treatment should not be reused, due to the possibility of bacterial contamination.	Avoid co-treatment with other medications. Do not use product if it appears incompletely dissolved or there is excessive turbidity. Do not use the product if it has been frozen. Any liquid remaining after treatment should not be reused, due to the possibility of bacterial contamination. When administering the product i.v., ensure that none of the medication leaks out of the blood vessel (in infants, if there is leakage during i.v. treatment, the skin near the insertion point may become ulcerated; cases of skin necrosis have been reported)
Storage		Store at <30°C; do not freeze		Store at ≤10°C; do not freeze	Store at <10°C; do not freeze
		Information based on revised product manual (May 2010)	Information based on revised product manual (April 2011)	Information based on revised product manual (September 2011)	Information based on revised product manual (June 2012)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CPK, creatine phosphokinase; IVIG, i.v. immunoglobulin; KD, Kawasaki disease.

(1) The sulfonated product (Kenketsu Venilon-I; Teijin, Tokyo, Japan) contains serum albumin, and its sodium concentration is identical to that of saline (154 mEq/L).
(2) The two products processed with PEG come in freeze-dried (Kenketsu Glovenin-I; Nihon Shinyaku, Kyoto, Japan) and liquid (Venoglobulin IH; Japan Blood Products Organization, Tokyo, Japan) form. The suggested infusion rate for PEG-processed IG is slightly slower than that of the sulfonated product. Kenketsu Glovenin-I has a sodium concentration of 154 mEq/L. Because liquid preparations are usually refrigerated until use, they must be warmed to at least room temperature beforehand.
(3) The pH 4-processed IG (Nisseki Polyglobin-N; Japan Red Cross Society, Tokyo, Japan) comes in liquid form and should also be warmed to at least room temperature before use. During injection, it is essential that the liquid does not leak out of the vein, because this may cause necrosis of the skin. Furthermore, because the preparation contains maltose, the plasma glucose dehydrogenase method should not be used to measure blood sugar after injection, given that this method can be affected by the presence of maltose.

Close monitoring and a slower infusion rate are required during the first 30–60 min, given that all the aforementioned products might result in anaphylaxis during treatment. If no adverse reactions occur during the first hour of treatment (rate, 0.01 mg/kg per min), the maximum rate (<0.03 mg/kg per min) of 2 g/kg may then be used over a course of 12–20 h.

IVIG retreatment for IVIG-resistant patients

Although IVIG is the established first-line treatment for KD, approximately 15–20% of all KD patients (16.6% of patients in the 21st Nationwide Survey of KD[1]) have persistent or recrudescent fever after 2 g/kg of IVIG, and there has been considerable debate regarding the optimal second-line treatment for such patients. The 21st Nationwide Survey of KD reported that additional IVIG was given to a large majority (91.5%) of the 3231 IVIG-resistant patients reported during the survey period. Steroid was given together with IVIG in 29.0% of patients, IFX in 4.3%, immunosuppressants in 3.7%, and PE in 2.2% of patients. IVIG retreatment alone was effective in approximately half of the patients.[24]

In recent years, various scoring systems have been developed to evaluate the likelihood of IVIG resistance at the time of diagnosis. Representative scoring systems are listed in Table 3.[8–10] If such scores suggest that patients are at high risk of IVIG resistance, more aggressive primary therapy in combination with the usual first-line treatment of 2 g/kg IVIG plus aspirin can be considered. In the RAISE study, Kobayashi *et al*. found that IVIG plus PSL, started at 2 mg/kg per day and halved every 5 days, was effective in preventing CAL formation and initial treatment failure.[8,13] In addition, Egami *et al*. and Ogata *et al*. as well as Sano *et al*. and Okada *et al*. reported the effectiveness of methylprednisolone (MP; 1–3 doses of 30 mg/kg of IVMP) in combination with IVIG.[9–12] As compared with patients receiving only IVIG plus aspirin, defervescence was significantly more likely, and the incidence of CAL was significantly lower, among patients receiving IVIG plus steroids. Although further research is necessary, it seems advisable to adapt this risk-stratified strategy for severe cases so as to reduce the number of IVIG-resistant patients and further lower the incidence of CAL.

Table 3 Representative scoring systems for evaluating potential IVIG resistance

	Cut-off point	Points
Kobayashi score[8] (≥5 points; 76% sensitivity, 80% specificity)		
Sodium	≤133 mmol/L	2
Day of illness at initial IVIG (= KD diagnosed)	Day 4 or earlier	2
AST	≥100 IU/L	2
Neutrophil ratio	≥80%	2
CRP	≥10 mg/dL	1
Platelet counts	$\leq 30.0 \times 10^4/mm^3$	1
Age	≤12 months	1
Egami score[9] (≥3 points; 78% sensitivity, 76% specificity)		
ALT	≥80 IU/L	2
Day of illness at initial IVIG (= KD diagnosed)	Day 4 or earlier	1
CRP	≥8 mg/dL	1
Platelet counts	$\leq 30.0 \times 10^4/mm^3$	1
Age	≤6 months	1
Sano score[10] (≥2 points; 77% sensitivity, 86% specificity)		
AST	≥200 IU/L	1
Total bilirubin	≥0.9 mg/dL	1
CRP	≥7 mg/dL	1

AST, aspartate aminotransferase; CRP, C-reactive protein; IVIG, i.v. immunoglobulin; KD, Kawasaki disease.

Effectiveness

I.v. immunoglobulin was found to be quite safe and, at present, has the greatest effectiveness. For these reasons, its effectiveness has been widely recognized both in Japan and in other countries, and it is also included in the recommendations of many relevant textbooks.

The incidence of cardiac complications reported in the latest Nationwide KD survey decreased to approximately half that in 1997–1998, when patients only rarely received 2 g/kg IVIG. During the acute phase of the illness, that is, until approximately 1 month after disease onset, the incidence of cardiac complications was 9.3%, including dilation, 7.26%; valvular insufficiency, 1.19%; coronary aneurysm, 1.04%; giant coronary aneurysm, 0.24%; coronary artery stenosis, 0.03%; and myocardial infarction, 0.01%. Even during the convalescent phase, that is, >28 days after disease onset, complications persisted in 3.0% of patients, including dilation, 1.90%; aneurysm, 0.78%; valvular insufficiency, 0.29%; giant aneurysm, 0.22%; stenosis, 0.03%; and myocardial infarction, 0.02%. Furthermore, the number of deaths in Japan within 2 years of KD onset was 51 during the 10 year period 1991–2000, which decreased by more than 60% to 19 cases with the introduction of 2 g/kg IVIG during the subsequent 10 year period, 2001–2010 (Fig. 2).[1]

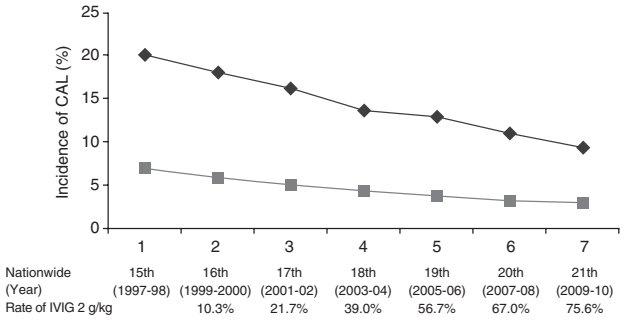

Fig. 2 Incidence of coronary artery lesions (CAL) vs rate of 2 g/kg i.v. immunoglobulin (IVIG) treatment. –◆–, <30 days; –■–, ≥30 days.

Side-effects

I.v. immunoglobulin is derived from human plasma and is considered to have very few adverse effects and a high level of safety (Table 4). It is necessary, however, to carefully explain the possibilities of rare side-effects to patients and/or their families and to obtain their informed consent before treatment.

In Japan, there have been no reports of viral contamination of any IVIG product. Donated blood is carefully screened to confirm the absence of HBs antigens, anti-HCV antibodies, anti-HIV-1 antibodies, anti-HIV-2 antibodies, and anti-HTLV-1 antibodies and to verify normal ALT. Furthermore, when plasma is pooled, the nucleic acid amplification testing (NAT) is used to test for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus, and human parvovirus B19, and only plasma that tests negative for all these infections is used. Using present pharmaceutical production processes, the absence of viruses that are undetectable even by NAT (e.g. abnormal prion proteins and human parvovirus B19), cannot be determined with 100% certainty, but there have been no reports of viral infection due to IVIG. Side-effects are infrequent but include post-treatment chills and shivering, shock (such as cyanosis and hypotension), anaphylactic reactions, aseptic meningitis,[25] hemolytic anemia,[26] hepatic dysfunction, jaundice, acute renal failure, thrombocytopenia, and pulmonary edema. Thus, patients should be careful monitored for these side-effects. Particularly immediately after the start of i.v. treatment and when the infusion rate is increased, the physician should monitor for coldness and shivering, altered consciousness, discomfort, trembling, cyanosis, hypotension, and shock. Finally, cardiac dysfunction or even acute heart failure may develop during acute KD, so close attention should be paid to patient vital signs, and to preventing sudden increases in circulating blood volume, throughout the duration of i.v. treatment.[27,28]

Other considerations when using IVIG are as follows.

(1) Patients with IgA deficiency: allergic reactions may occur in response to IVIG in patients with anti-IgA antibodies.
(2) Patients with renal damage: risk of further impairment of renal function.
(3) Patients with cerebral or cardiovascular damage or a history of these conditions: blood viscosity may increase when high-dose IVIG is given rapidly, thus leading to thromboembolic events such as cerebral or myocardial infarction.
(4) Patients at risk for thromboembolism: rapid use of high-dose IVIG could increase blood viscosity and lead to thromboembolic events.
(5) Patients with hemolytic anemia, blood loss anemia, immune deficiencies, or immunosuppressive disorders: the possibility of human parvovirus B19 infection cannot be completely excluded. If such infection occurs, severe systemic effects such as fever and sudden or persistent anemia may result.
(6) Patients with reduced cardiac function: high-dose IVIG may lead to cardiac dysfunction or could worsen existing heart failure.

A post-marketing survey of IVIG for KD noted that among 7259 patients who received IVIG treatment, 484 had a total of 697 adverse events (9.6%) and only 68 patients experienced 78 severe adverse events (1.1%; Table 5).[29]

Evidence levels

First-line IVIG treatment: class Ia, grade A.

Additional IVIG treatment in IVIG-resistant patients: class III, grade B.

Combined therapy with IVIG and steroid as first-line treatment for suspected IVIG-resistant patients: class Ib, grade B.

Table 4 General side-effects of immunoglobulin

	High incidence	Rare
General	Fatigue, fever, facial erythema, coldness	Anaphylaxis
Systemic side-effects	Loss of appetite, myalgia, arthralgia, swollen joints	Common cold symptoms, anaphylaxis, blepharedema
Neurological	Headache, migraine, dizziness	Aseptic meningitis, weakness, abnormal sensations
Respiratory	Shortness of breath, cough, bronchial spasms	Pleural effusion, blood transfusion-related lung disorders, pulmonary edema
Cardiovascular	Hypotension, hypertension, chest pain	Irregular pulse, myocardial infarction
Gastrointestinal	Loss of appetite, nausea, vomiting, abdominal pain, diarrhea	Taste disorder
Renal		Renal tubular disorders, renal failure
Dermatological	Urticaria, erythema, pimples, pruritus	Multiform exudative erythema
Hematological	Hemolysis	Thromboembolism, hyperviscosity syndrome, leukopenia

Table 5 Post-marketing survey of adverse effects of Ig for KD (no. treatments, 7259)

Side-effect	No. events
Hepatic dysfunction	69
Abnormal findings of liver enzyme tests	40
Pruritus, rash	78
Hypothermia	50
Hypotension	19
Aseptic meningitis	19
Pallor	15
Cyanosis	14
Heart failure	13
Shock	13
Peripheral coldness	13
Hemolytic anemia	4

KD, Kawasaki disease.

Methylprednisolone pulse

Purpose

I.v. methylprednisolone pulse is usually given because of its powerful and rapid immunosuppressive effect (Table 6). Among available steroids, MP treatment is often selected for high-dose i.v. infusion because it is less likely to disrupt electrolyte balance. IVMP is widely used in treating severe pediatric illnesses such as rheumatic disease and kidney disease and is also used in treating confirmed and suspected IVIG-resistant KD.

Mechanism of action

Steroids bind with glucocorticoid receptors in cytoplasm and regulate nuclear expression of proteins such as NF-κB, which produces an anti-inflammatory effect referred to as genomic action.[30] When high-dose MP is given i.v., however, the saturation point of these glucocorticoid receptors is greatly exceeded; thus, mechanisms other than genomic action are thought to contribute to its efficacy. Such mechanisms may include acting through proteins that dissociate from complexes with cytosolic glucocorticoid receptors, membrane-bound glucocorticoid receptors, and functional modification of membrane-bound protein after interlocation of the cell membrane. These mechanisms precede genomic action.[30,31]

When used for KD patients, the effects of IVMP are very rapid, which suggests that non-genomic mechanisms stimulate immunocytological activity and suppress inflammatory cytokines. In confirmed and suspected IVIG-resistant patients, IVMP was reported to limit production of cytokines involved in inflammation and CAL,[32] and to reduce transcription at the genetic level.[33]

Indications

Patients suspected of being IVIG resistant on the basis of clinical symptoms and laboratory findings.

Patients found to be IVIG resistant after first-line IVIG treatment.

It should be noted that IVMP treatment for KD is an off-label use.

Treatment method and dosage

In patients with kidney disease or connective-tissue disease, the standard dose of IVMP is 20–30 mg/kg IVMP, given once a day over a period of 2–3 h, for 1–3 consecutive days.[31] For KD patients, studies of IVMP in combination with first-line IVIG investigated a single dose of 30 mg/kg IVMP.[11,12,34] Studies of second-line IVIG treatment in IVIG-resistant patients investigated the same IVMP dose given once a day, for 1–3 days.[32,33,35–39] Because the half-life of IVMP is only 3 h,[31] some studies used additional therapy with PSL started at 1–2 mg/kg per day and gradually tapered over a period of 1–3 weeks.[38,39]

Effectiveness

First-line therapy with IVIG plus IVMP for all KD patients has not been proven to prevent CAL.[40] There is, however, no evidence that IVMP increases CAL incidence. In a double-blind randomized controlled trial comparing IVIG plus IVMP with IVIG plus placebo, no significant differences were found in factors such as duration of fever, incidence of additional treatment, incidence of CAL, and coronary artery diameter, as indicated by Z score.[34] A post-hoc analysis of patients requiring additional treatment, however, found that the incidence of CAL was significantly lower among those who had received IVIG plus IVMP, which suggests that the combined regimen had been effective among IVIG-resistant patients. Studies have also reported that suspected IVIG-resistant patients (as determined by Egami score or Sano score) who received first-line IVIG plus IVMP had earlier defervescence and a significantly lower rate of CAL than did those who had received IVIG alone.[11,12]

For patients resistant to initial IVIG, some studies compared IVMP as a second-line treatment to additional treatment with IVIG and found that duration of fever was shorter after IVMP but that CAL incidence was similar.[32,36–40] The researchers, however, highlighted the fact that IVMP therapy was less expensive than retreatment of IVIG.[36,37] Nevertheless, the finding of equal efficacy for IVIG and IVMP has not been shown in non-inferiority trials and requires confirmation. One study reported that IVIG-resistant patients who did not respond to additional IVIG had a lower rate of CAL after subsequent IVMP followed by PSL treatment.[39]

Side-effects

The reported side-effects of IVMP treatment for KD patients include sinus bradycardia (6–82%), hypertension (10–91%), hyperglycemia (6–55%), and hypothermia (6–9%).[39,41] Therefore, patient vital signs must be very carefully monitored during IVMP, including monitoring of electrocardiogram and blood pressure.

To avoid development of gastrointestinal ulcer, patients can be given H2 blockers and/or other antacid agents. Additional heparin can also be given as thrombosis prophylaxis.[38,39] Nevertheless, the necessity of these medications has not been proven.

Evidence levels

Initial IVIG plus IVMP for all KD patients: class Ib, grade C.

Table 6 Treatments other than IVIG for acute KD

General name	Mode of action	Treatment route, dose, and methods	Principal side-effects	Important notices
Methylprednisolone	Suppresses transcription of inflammatory proteins arising from glucocorticoid receptors Suppresses immune cells and inflammatory cytokines arising due to non-genomic activity, such as functional changes in cell membranes etc.	When used in combination with first-line IVIG: 1 dose of 30 mg/kg methylprednisolone. When used to treat IVIG-resistant patients: 30 mg/kg methylprednisolone once a day, for 1–3 days. Some reports suggest additional prednisolone (started at 1–2 mg/kg/day and gradually tapered over a period of 1–3 weeks) after methylprednisolone.	Sinus bradycardia (6–82%), hypertension (10–91%), hyperglycemia (6–55%), hypothermia (6–9%) etc. In rare cases, patients may develop infections, gastrointestinal ulcers, mental disorders, femur head necrosis, and suppressed adrenal function.	Vital signs – including electrocardiogram, body temperature, and blood pressure – should be continuously monitored
Prednisolone	Inhibits gene transcription of inflammatory proteins and promotes gene transcription of anti-inflammatory proteins	During fever: 2 mg/kg/day of prednisolone, i.v. in 3 divided doses After defervescence: Once patient is no longer febrile and general status has improved, prednisolone is given orally. When CRP normalizes, the dose of prednisolone is tapered over 15 days, in 5 day steps, from 2 mg/kg/day in 3 divided doses to 1 mg/kg/day in 2 divided doses to 0.5 mg/kg/day in a single dose.	Some viral infections (a few percent), moon facies (most who receive this treatment), hypothermia immediately after defervescence (a few percent), occult blood positivity (approx. 1%), hyperlipidemia (a large proportion), neutrophil-predominant leukocytosis (in almost all cases) etc. General side-effects of steroid treatment: infections, gastrointestinal ulcers, mental disorders, femur head necrosis, suppressed adrenal function etc.	
Infliximab	Neutralizes biological activity of soluble TNF-α Damages membrane-bound TNF-α-expressing cells, with complement- and antibody-dependent cell damage Dissociates TNF-α bound to TNF-α receptors	i.v. drip infusion of 5 mg/kg (may only be given once)	Of 708 adult cases in Japan, nasopharyngitis (19.6%), fever, (11%), exanthema (8.9%), headache (5.8%), cough (5.1%), elevated ALT (12.6%), elevated AST (9.9%), elevated LDH (9.3%) etc.	
Ulinastatin	Inhibits elastase release from neutrophils and platelets, and rendering it inactive after release	i.v. drip of 5000 units/kg, 3–6 times a day, for 3–4 days No treatment may exceed 50 000 units.	Anaphylaxis, hepatic dysfunction (0.5%), leukopenia (0.2%), allergic symptoms such as exanthema and pruritus (0.1%), diarrhea, angiodynia (0.1%), elevated AST, elevated ALT, eosinophilia, vascular pain at injection site etc.	Avoid mixing with IVIG in treatment route
Cyclosporine A	Suppresses cytokine production such as IL-2 by inhibiting nuclear factor of activated T cells	Start on 2 divided oral doses (1 each before meal) of 4–5 mg/kg/day Target trough level: 60–200 ng/mL	Subclinical hyperkalemia (with lower values in plasma than in serum; no reports of adverse events such as arrhythmia etc.) General adverse reactions include increased blood pressure, nausea and vomiting, shivering, hyperglycemia, hyperuricemia, hyperlipidemia (1–5%) etc.	
Methotrexate	Suppresses proliferation of several immunomodulatory cells by inhibiting synthesis of DNA as a folic acid antagonist	One oral dose of 10 mg/body surface area per week	Side-effects appearing at standard doses (gastrointestinal injury, hair loss, myelosuppression etc.) are not reported at lower doses	
Plasma exchange	Mechanical removal of inflammatory cytokines	Displacing solution set at 5% albumin; 1–1.5x the patient's circulating plasma volume is exchanged Usually given for 3 continuous days (upper limit: 6 days)	Hypotension, hypovolemia, shock, anaphylactoid reactions, hypocalcemia, fever/coldness/shivering, nausea/vomiting, coagulopathies, pneumothorax at time of catheter insertion	
Aspirin	Blocks synthesis of PGE2 from arachidonic acid during PG synthesis	Febrile period: Oral dose of 30–50 mg/kg/day, in 3 divided doses After defervescence: Single oral doses of 3–5 mg/kg/day	Bleeding, hepatic dysfunction, gastrointestinal ulcer, hematemesis, induction of asthmatic attacks, urticaria, exanthema (incidence unknown), loss of appetite (0.1 to < 5%), nephropathy (<0.1%) etc.	Special care should be taken when patient has chickenpox or influenza, as aspirin might induce Reye syndrome

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IL, interleukin; IVIG, i.v. immunoglobulin; LDH, lactate dehydrogenase; PG, prostaglandin.

Initial IVIG plus IVMP for suspected IVIG-resistant patients: class Ib, grade B.

Second-line IVMP use for IVIG-resistant patients: class IIb, grade B.

Prednisolone

Purpose

The primary purpose of PSL therapy is to take advantage of its powerful anti-inflammatory effects (Table 6). PSL may quickly resolve KD vasculitis and suppress the potential risk for remodeling of coronary arteries.

Mechanism of action

Prednisolone is the most widely used synthetic corticosteroid hormone, and its glucocorticoid action is stronger than that of cortisol. Through cytoplasmic steroid receptors, PSL inhibits gene transcription of inflammatory cytokines and promotes gene transcription of anti-inflammatory cytokines.[30] PSL also suppresses inflammation by inhibiting production of inflammatory cytokines (e.g. tumor necrosis factor-α [TNF-α], interleukin [IL]-6, IL-8), chemokines, and cell adhesion molecules. In addition, PSL stimulates production of anti-inflammatory proteins such as lipocortin, IL-1 receptor antagonists, β-2 adrenergic receptors, and IκB kinase.

Indications

Patients suspected of being IVIG resistant, based on evaluation of clinical symptoms and laboratory findings.

Patients found to be IVIG resistant after first-line IVIG treatment.

PSL treatment for KD is an off-label use.

Treatment method and dosage

When used in combination with initial IVIG, 2 mg/kg per day of PSL is given i.v. in three divided doses.[13] After defervescence and improvement in the patient's general condition, PSL can be given orally. After CRP normalizes, the patient is continued for 5 days on the same dosage in three divided doses of 2 mg/kg per day. Thereafter, if fever does not recur, the dosage of PSL is decreased to 1 mg/kg per day in two divided doses on the subsequent 5 days and then a single dose of 0.5 mg/kg per day on the final 5 days. If fever recurs after dose reduction, additional treatment should be considered, including an increase in PSL dose, IVIG retreatment, or other treatments. The most common periods for relapse are 4–5 days after the start of PSL and after the dose reduction from 2 mg/kg to 1 mg/kg.

For patients resistant to initial IVIG, the regimen for second-line PSL should, in principle, involve the same dosages and timings as specified for first-line PSL therapy.

Effectiveness

Although corticosteroids are the treatment of choice for other forms of vasculitis, their use has been limited in KD. In 1975, a case–control study showed that fatal cases were more frequently treated with PSL as compared with matched non-fatal cases.[42] In addition, a retrospective study found that PSL had a detrimental effect when used as initial therapy.[14] Finally, a prospective randomized controlled trial of three groups (receiving either aspirin, flurbiprofen, or PSL plus dipyridamole) did not confirm the efficacy of PSL. These results led to PSL being contraindicated for KD in the 1980s.[43] A retrospective study, however, in the 1990s of a PSL plus aspirin regimen found this combination to be useful in preventing CAL and shortening duration of fever,[44] which led to a reconsideration of PSL therapy. In 2006, a prospective randomized controlled trial comparing initial IVIG plus PSL to initial IVIG alone reported a significantly lower incidence of CAL in the IVIG plus PSL group.[45] A subsequent retrospective study suggested that risk stratification of initial treatment might be possible using the Kobayashi score;[8,46] therefore, a randomized controlled trial to assess immunoglobulin plus steroid efficacy for KD (RAISE study) was carried out. The RAISE Study showed that among patients with a Kobayashi score ≥5, initial treatment with IVIG plus PSL significantly decreased the incidence of CAL and rate of resistance to initial treatment.[13] Although its external validity remains unproven, initial therapy with IVIG plus PSL for patients at high risk of IVIG resistance could become the standard therapy for severe KD.

Reports have also shown the effectiveness of PSL as a second-line therapy for IVIG-resistant patients.[47] One study however, reported that PSL therapy might induce CAL formation in IVIG-resistant patients, given that more days have elapsed since the onset of illness.[48] No randomized controlled trials have assessed PSL therapy for IVIG-resistant patients; thus, the efficacy of PSL for this subgroup is unknown.

Side-effects

According to the product labeling, PSL may lead to side-effects such as shock (0.08%), infection (2.54%), Legg-Calvé-Perthes disease (0.36%), gastrointestinal perforation (0.02%), gastrointestinal hemorrhage (0.80%), gastrointestinal ulcer (0.02%), diabetes (3.95%), posterior subcapsular cataract (0.09%), pancreatitis (0.03%), congestive heart failure (0.02%), and impaired hepatic function (1.21%), as well as circulatory collapse, arrhythmia, secondary adrenocortical insufficiency, osteoporosis, myopathy, thrombosis, increased intracranial pressure, seizure, abnormal mental function, glaucoma, central serous chorioretinopathy, esophagitis, and jaundice (incidences unknown).

Prednisolone is contraindicated for patients with (i) infections for which there is no effective antimicrobial agent, such as systemic mycoses; (ii) severe infections accompanied by reduced renal function or chronic renal failure; or (iii) a history of acute myocardial infarction.

Evidence levels

Initial IVIG plus PSL for suspected IVIG-resistant patients: class Ib, grade B.

Second-line treatment for IVIG-resistant patients: class IIb, grade C.

Biologics (infliximab)

Purpose

The serum concentration of TNF-α is elevated in KD patients, and several reports have shown a significant association between KD severity and incidence of CAA. IFX suppresses inflammation by blocking the action of TNF-α (Table 6).

Mechanism of action

Infliximab was originally developed in mice as a mouse antibody with human TNF-α. IFX is a chimeric monoclonal antibody and is produced by bonding 25% V-region – a specific antibody derived from mice – with 75% C-region of the human immunoglobulin G1 κ-chain. Because each IFX molecule contains 25% mouse protein, anti-chimeric antibodies (neutralizing antibodies) develop in approximately 40% of patients; thus, among patients undergoing repeated use, its efficacy decreases and allergic reactions might occur. Production of neutralizing antibodies is inhibited in patients with rheumatoid arthritis (RA) who receive IFX in combination with MTX. IFX binds specifically to TNF-α, not to TNF-β. The mechanisms of action are believed to be as follows: (i) neutralize soluble TNF-α and block binding of TNF-α to TNF receptors (p55 and p75); (ii) bind membrane-associated TNF-α expressed on the surface of TNF-α-producing cells, inducing apoptosis through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity and inhibiting production of TNF-α; and (iii) dissociate TNF-α bound to receptors. As a result of these mechanisms, IFX suppresses activation of inflammatory cells and production of inflammatory cytokines such as IL-1 and IL-6.

Indications

IVIG-resistant patients.

The use of IFX for treating KD is off-label.

Treatment method and dosage

In Japan, IFX is presently approved for use in adults with (i) RA; (ii) inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis); (iii) intractable uveitis accompanying Behçet disease; (iv) pruritus; and (v) ankylosing spondylitis (AS). In Europe and the USA, it has also been approved for use in treating Crohn's disease in children aged ≥6 years.[49]

Children treated with IFX usually receive one dose of 5 mg/kg. In patients with Crohn's disease, however, there are reports of other dosages such as 3 mg/kg or 6 mg/kg. For adults with RA, 3–10 mg/kg IFX is given i.v. once every 8 weeks. IFX has a half-life of approximately 9.5 days and is usually given by i.v. drip infusion mixed in 200–500 mL of saline, over a period of at least 2 h. Unlike RA, KD is an acute disease, and MTX and steroids are not usually given as they would be for RA. A single-dose IFX regimen is recommended because KD is an acute disease, unlike RA, and MTX or steroids are not usually concomitantly used. Studies in the USA have not established a lower age limit for IFX use, but there is no assurance of complete safety when IFX is given to newborns and infants.

Effectiveness

The first experience of the effectiveness of IFX for treating KD was reported in 2004 by Weiss *et al*., who used it with positive results to treat a 3-year-old patient who had not responded to treatment with IVIG and IVMP at the 45th day of illness.[50] Later, several reports confirmed the effectiveness of IFX in suppressing inflammation among patients resistant to both IVIG and IVMP. These reports suggested that IFX is safe and effective within a relatively short time.[51–61] IFX lowered serum levels of inflammatory markers such as IL-6, CRP, and soluble TNF-α receptor 1.[52,62] By 2009, a total of 39 cases (patient age range, 1 month–13 years; CAA development, 22 of 39) of IFX use in treating KD that did not respond to IVIG and/or IVMP had been reported.[58] In the USA, IFX was used in approximately 1% of the 4811 IVIG-resistant cases, and its use had increased from 0% in 2001 to 2.3% by 2006.[63] In a recent review of additional treatment for IVIG-resistant patients, either additional IVIG, 3 days of IVMP, or IFX was recommended.[64] The effectiveness of anti-TNF-α antibody in reducing vasculitis severity was demonstrated in an animal model of KD vasculitis.[65]

In Japan, 6 years have passed since IFX was first used as an off-label treatment for a patient who failed to respond to IVIG.[52] The Japanese Society of Kawasaki Disease surveyed the use of IFX during 2006–2011 and found a total of 192 patients treated with IFX during that period. It was effective in around 80% of cases but was unsuccessful in reducing fever in 10–15% of cases. Experimental studies have not reported any severe side-effects; thus, IFX appears to be relatively safe for use in most patients. In general, the incidence of CAA is lower when IFX is used before the 10th day after onset.

Side-effects

After IFX had been approved for RA, it was given to >5000 adult patients with RA in Japan. Adverse events were reported in 28% of these patients within 6 months of first use; 6.2% of these were severe adverse events, including bacterial pneumonia (2.2%, 108 patients), *Pneumocystis* pneumonia (0.4%, 22 patients), sepsis (0.2%, 10 patients), tuberculosis (0.3%, 14 patients), and severe infusion reaction (0.5%, 24 patients; Table 7).[66–76] As for patients with juvenile idiopathic arthritis (JIA), there is a report that adverse events were more frequent at lower doses (3 mg/kg) than at higher doses (6 mg/kg).[69] There are limited data, however, on the safety of IFX in children. Therefore, the indication of IFX for KD should be determined only after carefully assessing the risk–benefit balance on a case-by-case basis.

Infusion-associated reaction

Because IFX is a chimeric monoclonal antibody, it might induce anaphylactic reactions. For this reason, patients receiving IFX should be carefully observed for symptoms such as fever, rash, pruritus, and headache, along with regular monitoring of vital signs. The patient should also be carefully monitored for other side-effects, such as respiratory distress, bronchial spasms, angioedema, cyanosis, hypoxia, and urticaria.[70]

Premedication with acetaminophen and/or antihistamines is considered ineffective for preventing anaphylactic symptoms.[70]

Table 7 Severe adverse effects and contraindications of anti-TNF-α treatment for children [66–76]

Severe adverse effects
Overresponse at treatment site
Infusion reaction
Varicella infection
Latent infections (tuberculosis etc.)
Neurological demyelination diseases (multiple sclerosis etc.)
Neuropsychiatric side-effects
Fatigue, headache, vertigo, depression, anxiety
Pain amplification syndrome
Malignant tumors
Immunogenicity
Contraindications
Complete contraindications
Active infections
Recurrent infections and history of chronic infections
Existing untreated tuberculosis
Multiple sclerosis, optic neuritis
Combined use with anakinra (anti-IL-1 receptor antagonist)
Active or recent (previous 10 years) malignant tumor (except skin tumors)
Relative contraindications
Pregnancy, breastfeeding
HIV, HBV, or HCV infection

IL, interleukin.

As for long-term IFX treatment, in a study of 163 patients with JIA (68 receiving IFX and 95 receiving etanercept; mean age, 17 years; mean treatment period, 22.9 months), there were 71 adverse events, and 62.9% of the events occurred in patients treated with IFX. In contrast, another report found IFX to be safe and well-tolerated, with few side-effects.[73] Among patients with JIA who had been receiving IFX for 1 year, the incidence of infusion reaction was 3.3% among those who had been receiving a dose of 3 mg/kg and 7% among those receiving 6 mg/kg.[74,75] In addition, neutralizing human antichimeric antibodies (HACA) were found in many patients who developed an infusion-associated reaction. HACA was also found in 7.1–12.1% of pediatric patients with Crohn's disease.[76]

Delayed hypersensitivity symptoms were seen ≥3 days after repeated use of IFX (24 h–3 weeks after treatment), including myalgia, rash, fever, fatigue, arthralgia, pruritus, edema of the hands and face, dysphagia, urticaria, pharyngeal pain, and headache. Table 7 lists the points of concern when giving IFX to pediatric patients. For these reasons, additional use of IFX in patients with acute KD is not recommended.

Exacerbation of heart failure

Infliximab worsened symptoms of heart failure in adults with New York Heart Association (NYHA) class III or IV disease and left ventricular ejection fraction <50%. Even among NYHA class II patients, IFX should be used with caution because serum brain natriuretic peptide is elevated in acute KD, which suggests asymptomatic cardiac impairment, including subclinical myocarditis, cardiac hypofunction, pericardial effusion, and atrioventricular valvular regurgitation.[70]

Exacerbation of infectious diseases

The possibility of worsening of infectious disease is especially important for infants who have not yet been vaccinated against BCG. QuantiFERON (QFT-TB Gold; Japan BCG Laboratory, Tokyo, Japan) testing is not affected by BCG vaccination or mycobacterial infection, but a false-positive result may occur if a patient has a history of past infection. Although pediatric patients sometimes show false-negative results, QuantiFERON testing may nevertheless be useful. It is essential to conduct a careful diagnostic interview, including questions on infections in family members and the patient's BCG vaccination status. Findings from chest radiography or computed tomography, if required, are also important.

As for live vaccines other than BCG, such as the rotavirus vaccine, use of IFX should be postponed if the patient has had such a vaccination <2 months previously or has had vaccines for measles–rubella, mumps, or chickenpox <1 month previously. IFX is contraindicated if any active infection is present.

Unfortunately, evidence is limited regarding the interval necessary between inoculation with a live vaccine and IFX treatment. Some specialists suggest an interval of 2–3 months to ensure patient safety.

Development of malignant tumors

When etanercept was used to treat 1200 patients with JIA, five patients developed malignancies, including Hodgkin lymphoma, non-Hodgkin lymphoma, thyroid carcinoma, yolk-sac cancer, and cervical dysplasia of the uterus. All these patients, however, had also been treated with other immunosuppressants, and two had received adalimumab and IFX as well. Before IFX is given, the possible side-effects should be carefully explained to the patient and/or family, and written informed consent should be obtained.[71] The US Food and Drug Administration reported that 48 patients developed malignant carcinomas (of which half were lymphomas) after receiving anti-TNF-α agents, and 11 patients died. Among the patients, IFX was given to 31, etanercept to 15, and adalimumab to two patients; 88% of the patients developing malignant carcinomas had also received other immunosuppressants (e.g. azathioprine and MTX).[72] The present data do not show a conclusive association between IFX and malignant disease.

Carriers of hepatitis B and C

Among adult patients with rheumatic diseases, asymptomatic carriers of HBV or chronic hepatitis may experience reactivation of HBV or de novo hepatitis.[77,78] Thus, testing for HBs antigens and HBs and HBc antibodies is necessary before IFX treatment. Because HBV carrier status and presence of chronic viral hepatitis are associated with higher risk of activation of these viruses and exacerbation of existing hepatitis, IFX use in such patients should be avoided, as recommended by the Japan College of Rheumatology.[78]

Screening for HCV infection should be done before IFX treatment. IFX is also contraindicated for patients with active hepatitis C. Patients who are positive for HCV but do not have active hepatitis should be carefully monitored if IFX is used. Although the safety of IFX for hepatitis C patients has not been confirmed,

there are no reports in Japan or other countries of IFX worsening hepatitis C. Nevertheless, consultation with a pediatric liver specialist is recommended before beginning IFX treatment.

Other

Infliximab is contraindicated in patients with demyelination disorders or allergy to IFX. For patients with KD, severe complications due to IFX are likely to be uncommon because IFX is mostly given as one dose and because KD patients usually have no other chronic active infectious disease. Many children, however, become susceptible to acute infectious disease at early infancy thus, IFX should be used only after careful examination for active infections such as pneumonia, otitis media, and urinary tract infections. In addition, long-term follow up of possible side-effects is required.

Evidence levels

When used for IVIG-resistant patients: class IIb, grade C.

Ulinastatin

Purpose

The principal action of UTI is to reduce inflammatory vascular lesions caused by proteolysis, edema, necrosis, and hemorrhage (Table 6).[79]

Mechanism of action

Ulinastatin is a human urinary trypsin inhibitor, purified from human urine. UTI is a polyvalent enzyme inhibitor – a serine protease inhibitor – with a molecular weight of 67 000 kDa and blocks various protein-degrading pancreatic enzymes, including trypsin. UTI is produced by many organs, including liver, kidney, pancreas, lungs, heart, adrenals, stomach, large intestine, brain, and testes.

Suppression of TNF-α

Ulinastatin suppresses production and secretion of inflammatory cytokines, for example TNF-α, IL-6, and IL-8 from neutrophils or TNF-α from monocytes.[80] It also inhibits expression of intercellular adhesion molecule-1 on the surface of vascular endothelial cells activated by TNF-α, thereby playing a protective role with regard to endothelial cells.

Blocking of neutrophil elastase

Ulinastatin has a dual action, first blocking elastase release, especially from neutrophils and platelets, and then deactivating elastase as it is released. UTI removes oxygen radicals and reduces the activity of cytokines and cell adhesion factors. By stabilizing lysosome membranes, UTI suppresses the release of various protein-degrading enzymes. Finally, it also blocks the release of inflammatory cytokines of myocardial inhibitory factor containing TNF-α and hypercoagulopathy.[81]

Indications

IVIG-resistant patients.

Initial treatment in combination with IVIG.

Its use in KD treatment is off-label.

Treatment method and dosage

Although optimal dosage has not been determined for pediatric patients, several reports show that a dose of 5000 U/kg given 3–6 times/day, not exceeding 50 000 units/dose, is suitable for KD patients. UTI has a half-life of only 40 min when given i.v. at 300 000 U/10 mL. UTI is officially approved to treat two conditions: (i) acute pancreatitis in the earlier phase (adult dosage, 25 000–50 000 units i.v. 1–3 times/day with dose tapering thereafter); and (ii) acute circulatory collapse (adult dosage, 100 000 units i.v. 1–3 times/day).

Effectiveness

Ulinastatin has been reported to inhibit mRNA transcription of prostaglandin H2 and thromboxane A2 in polynuclear leukocytes.[82] It also prevented neutrophil-induced damage to endothelial cells.[83] The first use of UTI was reported in 1993, after which several case studies were reported. These reports appeared to support the effectiveness and safety of UTI treatment under certain conditions, such as (i) when given as a single dose to patients with clinically mild disease; (ii) when it allowed a reduction in IVIG dose in the context of combination therapy; and (iii) when IVIG was ineffective due to non-response or resistance to IVIG.[84,85] Although these studies enrolled only a small number of patients, and there have been no well-designed clinical studies of UTI, it has been recognized and used as an additional option for treating IVIG-resistant patients.[86] Recent retrospective cohort studies showed that as a first-line treatment UTI in combination with IVIG plus aspirin was less likely to require second-line treatment and had a lower risk of CAA among patients at high risk for IVIG resistance, as defined by Kobayashi score.[87]

Side-effects

The most important side-effect of UTI is anaphylactic shock. UTI should be used carefully if the patient has a history of drug allergies or allergic reactions to products containing gelatin or a past history of UTI use. Other side-effects include liver dysfunction (0.5%), leukopenia (0.2%), rash, pruritus (0.1%), diarrhea (0.1%), angialgia (0.1%), increased AST and/or ALT, eosinophilia, and vascular pain at the injection site. Also, if UTI is given along the same route as IVIG and the medications are thus mixed, the drug will become white and turbid. To avoid this, a different i.v. route can be selected. Alternatively, IVIG may be paused and the i.v. route can be flushed with saline before and after UTI infusion, after which IVIG infusion can continue.

Evidence level

First-line treatment with IVIG plus UTI: class IIa, grade B.

IVIG-resistant patients: class IIb, grade C.

Immunosuppressants

Cyclosporin A

Purpose

In 2008, Onouchi *et al*. reported a susceptibility gene of KD: inositol 1,4,5-trisphosphate 3-kinase C (*ITPKC*), composed of

inositol triphosphate (Table 6).[88] ITPKC suppresses T-cell activity through the calcineurin/nuclear factor of activated T-cells (calcineurin/NFAT) cascade. Patients with suppressed ITPKC function may produce more cytokines, such as IL-2. For this reason, ITPKC was thought to be a critical gene contributing to IVIG resistance and development of CAA. CsA is used to block calcineurin function and suppress cytokine production.

Several studies evaluated the efficacy of CsA in IVIG-resistant patients.[89–91] Accumulating evidence of its effectiveness spurred multicenter observational studies in Japan and other countries, and the results of these studies indicate that CsA is safe and well-tolerated.[90,91]

Mechanism of action

Cyclosporin A binds and inhibits calcineurin, which has a major role in signal transduction that results in increased T-cell activity. By dephosphorylating NFAT, the transcription factor for IL-2 genes, the nuclear import of NFAT is blocked, and production of cytokines such as IL-2 is inhibited.[92]

Indications

IVIG-resistant patients.

Its use in treating KD is off-label.

Treatment method and dosage

Usually, 4 mg/kg per day of Neoral® (Novartis Pharmaceuticals UK, Surrey, UK) is given orally in two divided doses before meals.[90] The required dose is drawn into a 1 mL syringe and can be given to infants. Outside Japan, some researchers believe that the absorption of CsA is reduced during acute KD. Thus, they start patients on i.v. 3–5 mg/kg per day. After resolution of fever, 10 mg/kg per day of Neoral is given orally in two divided doses of 5 mg/kg.[91] In principle, before the fifth dose on the third day, the trough level of CsA should be monitored to confirm that it is within the therapeutic range (60–200 ng/mL). If it is not within the therapeutic range and fever remains, the dose may be increased by 5–8 mg/kg per day.[90] There is no established duration of treatment, but CsA is usually given until CRP again normalizes, or for a period of 10–14 days. This period may be extended if the dose is tapered.[91] Therapeutic doses of aspirin 30–50 mg/kg per day should be given in combination with CsA until defervescence is confirmed.

Effectiveness

Cyclosporin A has not been evaluated in prospective randomized trials, but observational studies of its use as a third-line treatment in IVIG-resistant patients showed that fever was reduced within 72 h in most patients receiving CsA, and CRP returned to normal.[90,91] Additional IVIG, however, was occasionally required for cases in which CsA was ineffective.[90] It should be noted that there are no reports of its use in infants younger than 4 months.[90,91]

Side-effects

There have been no reports of severe side-effects in treating KD. In approximately 40% of patients, asymptomatic hyperkalemia was observed in serum samples 3–7 days after treatment. Because plasma samples did not show evidence of hyperkalemia, these may have been cases of pseudohyperkalemia.[90] There have also been reports of hypomagnesemia,[91] but no reports have noted arrhythmias due to electrolyte imbalances. Other side-effects reported in patients receiving long-term CsA include hirsutism and hypertension in a few patients.

Evidence level

Class III, grade C.

Methotrexate

Purpose

In 2008, Lee *et al*. reported that MTX reduced fever and suppressed inflammation in IVIG-resistant patients.[93]

Mechanism of action

Methotrexate (4-amino-N10-methylpteroyl glutamic acid) is a folic acid antagonist. Pharmacologically, MTX (i) inhibits synthesis of purine bodies; (ii) increases adenosine release; (iii) inhibits production of inflammatory cytokines; (iv) suppresses lymphoproliferation; and (v) suppresses migration and adhering of neutrophils; and (vi) suppresses serum immunoglobulin. The mechanism by which low-dose MTX suppresses inflammation, however, has not been confirmed.

Indications

IVIG-resistant patients.

Use of MTX in treating KD is off-label.

Treatment method and dosage

Dosage: 10 mg/m^2, given orally once a week. Do not provide folic acid supplements. MTX is given until defervescence. In the report by Lee *et al*. describing the use of MTX, the median total dosage was 20 mg/m^2(range, 10–50) given in two divided doses.[93]

Effectiveness

Although there have been no prospective randomized trials of MTX, in a case series describing 17 IVIG-resistant patients who received MTX, fever recurred 7 days after the start of MTX in three patients and 14 days after the start of MTX in one patient. Fever resolved, however, in all four of these patients after they received their second or third dose of MTX. Finally, there was no fever recurrence after MTX was discontinued.

Side-effects

The side-effects of MTX at standard doses include gastrointestinal disturbances, hair loss, and myelosuppression, but these side-effects were not seen at low doses.[93] In general, side-effects could include shock or anaphylaxis, myelosuppression, infection, hepatic dysfunction, and acute renal failure.

Evidence levels

Class III, Grade C.

Plasma exchange

Purpose

Plasma exchange directly removes cytokines and chemokines from blood and induces quick recovery from cytokine storm (Table 6).

Mechanism of action

Cytokine storm is thought to be a major contributor to KD pathology. PE might reduce this inflammatory reaction by removing soluble cytokines, even in IVIG-resistant patients. After PE, the serum level of cytokines and chemokines, especially IL-6 and soluble TNF receptor, is markedly reduced.

Indications

IVIG-resistant patients.

Treatment method and dosage

The replacement solution is 5% albumin, and the total volume to be exchanged is approximately 1–1.5-fold the circulating plasma volume (mL), calculated as follows: [bodyweight (kg)/13 × (1–Hct/100) × 1000] (Hct, hematocrit [%]). Treatment is via the femoral vein, subclavian vein, or internal or external jugular veins, using a 6–7 Fr pediatric dialysis double-lumen catheter. During treatment, heparin 15–30 U/kg, first as a bolus i.v. infusion and 15–30 U/kg per h thereafter, may also be given for its anticoagulant effect, with the activated clotting time adjusted to 180–250 s. It is also necessary to keep the patient sedated.

Effectiveness

There have been no prospective randomized trials of PE for treatment of pediatric diseases, including KD. Two retrospective studies assessed the effectiveness of PE.[94,95] One compared PE with IVIG given to 20 patients within 15 days of KD onset.[96] Although the findings were not statistically significant, no patients developed CAL, and there were no adverse effects.

In studies of the safety and efficacy of PE, multivariate analysis comparing PE with additional IVIG yielded an odds ratio of 0.052 and showed a significant reduction in CAL incidence among PE patients.[97,98] Among PE-resistant patients, some already had CAL. Thus, to ensure optimal outcome PE should probably be started before development of CAL.[99]

Side-effects

In general, the side-effects of PE include hypotension, hypovolemia, and shock. In addition, the replacement solution (in the case of fresh frozen plasma) might induce urticaria, allergic reactions, anaphylactic reactions, and hypocalcemia, as well as fever, chills, shivering, nausea, vomiting, and coagulopathies.[100]

Because the volume of extracorporeal circulation will exceed circulating blood volume in pediatric patients, it may be necessary to reduce the volume to lower the risk of hypotension.

Evidence level

Class III, grade C.

Antiplatelets/anticoagulants

Aspirin

Purpose

Because the mechanism of action of aspirin differs by dosage, medium–high doses are usually given to treat KD in the febrile phase, due to decreased absorption and hypoalbuminemia, to obtain the expected anti-inflammatory benefits (Tables 6, 8). Low doses, however, are usually given to inhibit platelet aggregation after the febrile phase, when the risk of CAA is much lower.

Mechanism of action

Aspirin irreversibly inhibits platelet aggregation to block synthesis of thromboxane A2 by cyclooxygenase-1 activity. It also exerts an anti-inflammatory effect by blocking synthesis of prostaglandin E2 from arachidonic acid during prostaglandin synthesis.

Indications

Approved for all patients.

Treatment method and dosage

Aspirin is given orally. In the USA, high-dose aspirin 80–100 mg/kg per day is usually given in combination with IVIG as an initial treatment.[101] In Japan, a moderate dose of 30–50 mg/kg per day is usually given in three divided doses per day, together with IVIG. Thereafter, 48–72 h after defervescence, dosage can be reduced to one dose of 3–5 mg/kg per day. Even among patients without CAA, aspirin is typically continued for 6–8 weeks after onset of symptoms.

Effectiveness

Two meta-analyses in the late 1990s showed that CAA incidence was not associated with aspirin dose, although it was associated with IVIG dose and IVIG effectiveness.[102,103]

Side-effects

High-dose aspirin is associated with hemorrhage, asthma attacks, impaired liver function, and gastrointestinal ulcers (incidence rates unknown). Other side-effects include hematemesis, urticarial, rash (incidence rates unknown), loss of appetite (0.1 to <5%), and renal impairment (<0.1%). Hepatic dysfunction is common, so routine testing of liver enzymes is necessary. If abnormalities are found, it is necessary to reduce the dose or temporarily cease treatment. In children with chickenpox or influenza, it is important to be aware of the possible development of Reye syndrome. Current evidence does not indicate an increased risk of Reye syndrome among children receiving long-term low-dose aspirin after acute KD, but these patients should receive influenza vaccinations to ensure safety.

Evidence level

Initial therapy with IVIG plus aspirin: class Ia, grade A.

Other antiplatelet medications

Flurbiprofen (Froben®)

A total of 3–5 mg/kg per day, in three divided doses.

Table 8 Antiplatelet, anticoagulant, and thrombolytic drugs

Name of medication (trade name)	Mechanism of action	Dose and method of treatment	Side-effects (%)	Important considerations
Flurbiprofen	Anti-inflammatory effect by inhibiting cyclooxygenase	3–5 mg/kg, in 3 divided doses	Gastric discomfort (1.56%), loss of appetite (1.03%), rash (0.24%), rare cases of thrombopenia etc.	
Dipyridamole	Inhibits phosphodiesterase	2–5 mg/kg, in 3 divided doses	Headache (0.91–4.37%), palpitations (0.43–0.56%); severe side-effects: worsening of angina symptoms (<0.1%), tendency to bleed (incidence unknown) etc.	
Ticlopidine	Suppresses antiplatelet coagulation; reinforces activity of platelet adenylate cyclase	2–5 mg/kg, in 3 divided doses	TTP, agranulocytosis, severe liver damage (incidence unknown) etc.	Indications for treatment should be carefully examined. Blood tests required every 2 weeks during initial treatment.
Unfractionated heparin	Displays anticoagulant activity by binding AT-III, a factor in physiological inhibition of coagulation factors II, VII, IX, X, XI, XII	Start patient on slow i.v. 50 units/kg (duration of treatment: ≥ 10 min), then continuous i.v. infusion with 20–25 units/kg /h	Hemorrhage is the principal side-effect (incidence unknown) HIT (incidence unknown), impaired hepatic function (0.1 to <5%), rash (incidence unknown), hair loss/vitiligo (incidence unknown) etc.	APTT should be controlled within 60–85 s (1.5–2.5× that of controls)
LMWH	Displays anticoagulant effect through AT-III indirectly	Infants <12 months Treatment: 300 units/kg/day in 2 divided doses (every 12 h) Prevention: 150 units/kg/day in 2 divided doses (every 12 h) Children/adolescents Treatment: 200 units/kg/day in 2 divided doses (every 12 h) Prevention: 100 units/kg/day in 2 divided doses (every 12 h) Subcutaneous injection	Lower incidence of hemorrhage than unfractionated heparin Subcutaneous bleeding (3.8%), HIT (0.4%), headache/vertigo (1 to <10%), constipation/diarrhea (1 to <10%), abnormal hepatic functioning (1 to <10%) etc.	APTT should be controlled within 60–85 s (1.5–2.5× that of controls)
Warfarin	Achieves anticoagulant effect by inhibiting biosynthesis of vitamin K-dependent coagulation factors II, VII, IX, and X	0.05-0.12 mg/kg, in a single dose Orally	Hemorrhage (incidence unknown), allergic reactions (incidence unknown), impaired hepatic function/jaundice (incidence unknown) etc.	PT-INR should be adjusted to 1.6–2.5 and thrombotest to 10–25% Because warfarin is passed through the placenta, it is contraindicated for pregnant women in their first trimester
Urokinase	Degrades fibrin and encourages activation of plasmin	Systemic treatment 10 000–16 000 units kg (maximum 960 000 units), given in an i.v. drip over 30–60 min Intracoronary thrombolysis 4000 units/kg over 10 min, maximum 4 times	Hemorrhagic cerebral infarction (0.1 to <0.5%), cerebral hemorrhage (<0.1%), gastrointestinal hemorrhage (<0.1%), impaired liver function (<0.1%), rash and other allergic reactions (<0.1%) etc.	Additive effect with heparin, warfarin, aspirin, dipyridamole, ticlopidine hydrochloride, and other t-PA medications, leading to increased risk of hemorrhage When given with aprotinin medications, urokinase may have weakened capacity for fibrinolysis
Alteplase	Degrades fibrin and enhances activation of plasmin	290 000–435 000 units/kg; first administer 10% of total volume of medication i.v. for 1–2 min, and the remaining volume by i.v. drip over 60 min	Tendency to bleed, including cerebral hemorrhage (0.4%), gastrointestinal hemorrhage (0.6%), pulmonary hemorrhage (0.08%). After reperfusion, arrhythmias such as premature ventricular contraction, ventricular tachycardia, and ventricular fibrillation (incidence unknown), shock/anaphylactic symptoms (0.1%), abnormal hepatic function (0.1 to <0.5%) etc.	Increased risk of hemorrhage when given with other thrombolytics, anticoagulants, antiplatelet medications etc.
Monteplase	Its half-life, affinity for fibrin, and plasminogen activator activity are greater than those of alteplase	27 500 units/kg, i.v. over 2–3 min	Cerebral and gastrointestinal hemorrhage (0.1 to <5%), tendency to bleed including pulmonary hemorrhage (incidence unknown), cardiac rupture/perforation of intraventricular septum (0.1 to <5%). After reperfusion, arrhythmias such as premature ventricular contraction, ventricular tachycardia, and ventricular fibrillation (incidence unknown), shock/anaphylactic symptoms (0.1%), abnormal hepatic function (0.1 to <0.5%) etc.	Same as above
Pamiteplase	Same as above	65 000 units/kg, i.v. over 1 min	Severe bleeding, including cerebral hemorrhage, retroperitoneal hemorrhage, gastrointestinal hemorrhage etc (0.1 to <5%), cardiac rupture/cardiac tamponade (0.1 to <5%), ventricular tachycardia/ventricular fibrillation (0.1 to <5%), shock (<0.1%).	Same as above

APTT, activated partial thromboplastin time; AT-III, anti-thrombin III; HIT, heparin-induced thrombocytopenia; IVIG, i.v. immunoglobulin; LMWH, low-molecular-weight heparin; PT-INR, prothrombin time international normalized ratio; TTP, thrombotic thrombocytopenic purpura.

Flurbiprofen is sometimes given instead of aspirin for patients with severely impaired hepatic function, but there is insufficient evidence of its effectiveness. Furthermore, in patients with hepatic dysfunction related to onset of acute KD, such dysfunction often resolves after IVIG treatment.

Side-effects include epigastric discomfort (1.56%), loss of appetite (1.03%), rash (0.24%), and, rarely, thrombopenia.

Dipyridamole (Persantin® tablets, Anginal®)

A total of 2–5 mg/kg per day, in three divided doses.

Dipyridamole is sometimes given in combination with aspirin for patients with CAA. Its adverse events include headache (0.91–4.37%) and tachycardia (0.43–0.56%); more severe side-effects include worsening of angina symptoms (<0.1%) and hemorrhage (incidence unknown).

Ticlopidine (Panaldine®)

A total of 2–5 mg/kg, in three divided doses.

Ticlopidine is sometimes used to treat patients with CAA. The incidence of side-effects is unknown, but reported adverse events include thrombotic thrombocytopenic purpura and agranulocytosis, and severe liver damage may develop up to 2 months after treatment and is sometimes fatal. Therefore, indications should be carefully examined before use. During treatment, patients should undergo blood testing at least every 2 weeks.

Clopidogrel (Plavix®)

A total of 1.0 mg/kg per day, as a single dose (for patients aged 0–24 months, 0.2 mg/kg per day).

Clopidogrel is sometimes used in treating patients with CAA. The mechanism of action is similar to that of ticlopidine, although the incidence of liver damage is lower for clopidogrel. Sufficient antiplatelet action is achieved at a dose of only 0.2 mg/kg per day in patients aged 0–24 months.[104] Unfortunately, there are no data for patients aged ≥25 months; some centers use a dose of 1.0 mg/kg per day for these patients.

Use of the antiplatelet medications flurbiprofen, dipyridamole, ticlopidine and clopidogrel for treating KD is off-label.

Other cardiovascular agents

Anticoagulants

The coagulation/fibrinolytic systems are activated during the acute phase of KD. Therefore, patients with CAA require some form of anticoagulant to counteract this, although patients without CAL usually do not require anticoagulant treatment in the convalescent phase. Warfarin is widely used as an oral anticoagulant but, among patients requiring urgent treatment, i.v. unfractionated heparin (UFH) later switched to warfarin is the treatment of choice.

Warfarin

Warfarin prevents formation of intra-aneurysmal thrombi caused by increased activity in the coagulation/fibrinolytic system.

Mechanism of action

Warfarin blocks synthesis of vitamin K-dependent blood coagulation factors II, VII, IX, and X in liver.

Recent comprehensive genetic studies of the warfarin metabolic enzyme found that stable dosing of warfarin is related to genetic polymorphisms, including 30 different alleles, such as CYP2C9. Of these, the genotypes of CYP2C9*2 and *3 seem to be most affected by warfarin. CYP2C9*3, a poor metabolizer genotype, is prevalent among Japanese people; thus, warfarin dosage may need to be reduced in Japanese patients.[105]

Indications

Patients with medium–giant CAA.
Patients with a history of acute myocardial infarction.
Patients with a history of thrombogenesis in a CAA.

Treatment method and dosage

To achieve stable dosing, the patient can be started on 0.05–0.12 mg/kg per day o.d., which is increased to the optimal dosage in 4–5 days. Prothrombin time (PT) and the international normalized ratio (PT-INR) screens for coagulant factors II, V, VII, and X are useful for estimating the optimal dose of warfarin. In patients with KD, warfarin dosage should be adjusted so that the PT-INR is 1.6–2.5 (Thrombotest values: 10–25%).[106] In addition, the American Heart Association (AHA) KD Guidelines recommend a dose of 0.05–0.34 mg/kg warfarin, which is then adjusted to maintain PT-INR between 2.0 and 2.5.[101]

Usefulness

There have been no large-scale studies of the efficacy of warfarin. In CAA, and particularly in giant CAA, thrombi frequently form because of reduced shear stress, due to impaired vascular endothelial function and increased platelet count and aggregation.[107] In such cases, oral warfarin treatment is sometimes impossible because the patient's general status is unfavorable. These patients may require continuous infusion of UFH. After the anticoagulant effect induced by UFH has been confirmed, patients can be switched to oral warfarin. *Natto* (Japanese fermented soybeans), chlorella, and green and yellow vegetables contain significant amounts of vitamin K and may decrease the effectiveness of warfarin, as may commercial infant formula fortified with vitamin K. Breast-fed infants require special attention because of overdosing. Other medications may also influence the effectiveness of warfarin. Trimethoprim–sulfamethoxazole combinations, acetaminophen, antimicrobials such as erythromycin, antifungals such as fluconazole, anabolic steroids, amiodarone, and statins enhance the effect of warfarin. In contrast, the effects of warfarin may be reduced in patients taking phenobarbital, carbamazepine, or rifampicin.

Side-effects

The major side-effect of warfarin is hemorrhage. Epistaxis and gingival hemorrhage are common. The patient should also be carefully monitored for intracranial and intraperitoneal hemorrhage. Warfarin, which passes through placenta, is contraindicated for use in pregnant women due to the possibility

of embryopathies such as dysostosis/dyschondroplasia, central nervous system disorders, and microcephaly. The incidence of embryopathies is reported to be around 5%, and the risk is even lower at a dose of ≤5 mg/day.[108]

Evidence level

Class IIb, grade C.

Unfractionated heparin

Unfractionated heparin is obtained from the intestinal mucosa, liver, and lungs of healthy animals. It achieves its anticoagulant effect by binding to anti-thrombin III (AT-III), a physiological inhibitor of many clotting factors (II, VII, IX, X, XI, XII). The effective half-life of UFH is 1–2 h. An initial dose of 50 U/kg should be given i.v. over a period of 10 min or longer, which may be followed by a dose of 20–25 U/kg per h, to maintain an activated partial thromboplastin time (APTT) of 60–85 s (1.5–2.5-fold the APTT in controls). Infants may need proportionately larger doses than older children or adults.

There is insufficient evidence of the effectiveness of UFH when given to patients with acute KD. For patients with CAA at very high risk of thrombus formation, however, UFH should first be given as a continuous i.v. infusion, after which it may be switched to oral warfarin after the anticoagulant effect induced by UFH has been confirmed. The most significant side-effect is hemorrhage; other side-effects include heparin-induced thrombocytopenia (HIT), hepatic dysfunction, rash, diarrhea, and hair loss. Long-term UFH may cause osteoporosis.

Evidence level

Class III, grade C.

Low-molecular-weight heparin

Low-molecular-weight heparin (LMWH) achieves its anticoagulant effect along the same pathway as UFH. As compared with UFH, its inhibition of thrombin is weaker. In addition, the incidences of side-effects such as HIT and osteoporosis are lower. Enoxaparin, an LMWH, was found to be safe and effective for coronary intervention/thrombolytic therapy in adult patients with acute coronary syndrome.[109]

Evidence level

Class III, grade C.

Thrombolytics

Purpose

Patients with large CAA have a higher risk of acute coronary syndrome. Most KD-related acute myocardial infarctions occur within 2 years of KD onset, and most of these events result from the formation of new thrombi.

Thrombolytic therapy is indicated when a thrombus is detected in a CAA or when thrombotic occlusion and myocardial infarction develop. In adults with acute myocardial infarction, the treatment of choice is almost always percutaneous coronary intervention. At present, thrombolytics have an important role in clinical practice, and earlier treatment is associated with better results. American College of Cardiology/AHA guidelines state that it is best to start the patient on thrombolytic therapy within 12 h of thrombotic events.[110]

Mechanism of action

Thrombolytics are proteins belonging to the plasminogen activators (PA), enzymes that stimulate the activity of the fibrinolytic system. Activation of the fibrinolytic system is started by conversion of plasminogen to plasmin. Increased plasmin enzyme activity leads to catabolization of fibrin (a component of thrombi) and thrombolysis. Plasmin also catabolizes fibrinogen (the precursor of fibrin), which can induce hemorrhaging. The thrombolytics are classed as follows.

(1) First-generation thrombolytic: urokinase.
(2) Second-generation thrombolytics: tisokinase and its genetically modified analog alteplase are tissue plasminogen activators (tPA). They have a stronger affinity than first-generation thrombolytics for fibrin (a component of thrombi) and an enhanced thrombolytic effect. This category also includes nasaruplase, the precursor of the fibrinolytic agent urokinase.
(3) Third-generation thrombolytic: the further refined tPA monteplase has a longer half-life and even greater affinity for fibrin and results in greater plasminogen activation.

Thrombolytics are currently given systemically or for intracoronary thrombolysis (ICT). The research committee recommends systemic treatment with thrombolytics, which may be followed by ICT if necessary.

Indications

Patients with acute myocardial infarction or intra-aneurysm thrombi.

Patients with sudden enlargement of thrombi in a coronary artery.

Their use in KD patients is off-label.

Treatment method and dosage

The safety of thrombolytics has not been established in pediatric patients. Furthermore, because there is insufficient clinical evidence to recommend suitable standards, dosages, and treatment methods for pediatric patients, the following reference values for adult patients are included.

Urokinase. Covered by the Japanese health insurance system when given to adults as thrombolytic therapy for coronary thrombosis in cases of acute myocardial infarction. Although urokinase is the only thrombolytic also covered for use in ICT cases, however, it is almost never used in such cases.

Systemic i.v. treatment: 10 000–16 000 units/kg urokinase; upper limit, 96 000 units i.v. over a period of 30–60 min.

ICT: 4000 units/kg urokinase, injected over a period of 10 min. Maximum of four doses.

Alteplase (Activacin®, Grtpa®). Systemic i.v. treatment: 290 000–435 000 units/kg, 10% of which should be first given

i.v. over a period of 1–2 min, after which the remaining dose may be given by i.v. infusion over a 60 min period.

Monteplase (Cleactor®). Systemic i.v. treatment: 27 500 units/kg, i.v. over 2–3 min.

Effectiveness

Evidence of effectiveness is insufficient because no large-scale study has evaluated thrombolytic therapy in KD patients. Theoretically, as in adult patients, thrombolytic therapy should be used as an acute-phase therapy when required, to hasten reperfusion.[111–113] After systemic use of thrombolytics, recanalization occurs in 70–80% of patients. When ICT is added, these rates improve by approximately 10%.[106]

Side-effects

When reperfusion is achieved in cases of acute myocardial infarction, reported side-effects include arrhythmias such as paroxysmal ventricular contraction, ventricular tachycardia, and ventricular fibrillation, and even cardiac rupture. There is a tendency toward bleeding, including hemorrhage from the catheter insertion point, hematuria, and gingival hemorrhage. Digestive symptoms such as nausea and vomiting have also been reported. Furthermore, gelatin is used as a stabilizer in the formulation of urokinase; therefore, shock or anaphylactic symptoms may occur (including during tPA treatment). Before using these drugs, the patient's history should be carefully investigated, and his/her progress carefully monitored after treatment has begun.

When anticoagulants such as heparin and warfarin are given in combination with antiplatelets such as aspirin, dipyridamole, ticlopidine hydrochloride, or other tPA medications, an additive effect may increase bleeding tendency. Thus, in cases of combined use, coagulation tests (clotting time, PT) should be performed regularly and all clinical data carefully monitored. Conversely, co-treatment with aprotinin and urokinase could inhibit the fibrinolytic capacity of the latter.

Evidence level

Class IIb, grade C.

Anti-anginals and coronary vasodilators

Angina symptoms are extremely rare during the acute phase of KD, and patients with such symptoms are typically aged 1–2 years and thus cannot easily explain their symptoms to caregivers. In adult patients, the characteristics of angina symptoms may allow classification of angina as stable or unstable.

The principal therapeutic goal for angina is to reduce heart rate (thereby reducing cardiac workload), decrease preload and afterload, and increase coronary artery flow. For these reasons, beta-blockers, calcium antagonists and nitrovasodilators may be useful.

(1) Beta-blockers are the first choice for stable effort angina. To avoid side-effects in other body organs, beta-blockers that selectively block β-1 are recommended. As well as reducing myocardial workload and suppressing oxygen consumption, beta-blockers increase coronary blood flow accompanying bradydiastole, thereby preventing development of myocardial ischemia. Although atenolol, bisoprolol, and metoprolol have all been found to be effective,[114] beta-blockers may worsen prognosis in patients with coronary vasospasm, because upregulated α-receptor function may induce exacerbation of coronary tonus and symptoms of coronary spastic angina.[115] Carvedilol is a non-selective beta-blocker that also blocks α-1, and it increases coronary flow by lowering peripheral resistance in coronary arteries.[116]

(2) Calcium antagonists suppress the flow of Ca^{2+} into vascular smooth muscle cells. They are therefore extremely useful in preventing coronary vasospasm and are the first choice in treating coronary spastic angina.[117] KD-related myocardial infarction often occurs during sleep and may be induced by coronary spasms.[118] The ability of calcium antagonists to protect cardiovascular function seems to be due to stimulation of NO production. Because diltiazem blocks the L-type Ca^{2+} channel in cardiac myocytes, however, it is contraindicated for use in newborns up to early infancy.

(3) Nitrates exert their effect by dilating coronary arteries and reducing preload. Nitrates increase coronary blood flow and reduce both preload and afterload, which reduces the workload of the left ventricle, thereby relieving myocardial ischemia. Acute KD, however, is characterized by persistent damage to endothelial cells. Therefore, nitrates may not be effective in dilating impaired coronary arteries. A sublingual tablet of nitroglycerine or an oral spray of nitroglycerine or isosorbide dinitrate may alleviate angina symptoms. Nitrovasodilators are contraindicated in patients with glaucoma, in those taking phosphodiesterase inhibitors, and in those with cardiogenic shock, severe hypotension, or severe anemia.

(4) Nicorandil is a hybrid medication (a nitrovasodilator that opens the ATP-sensitive potassium channel) and can selectively dilate coronary arteries and inhibit coronary vasospasm.[119] It is therefore useful in preventing angina. Nicorandil also affects mitochondria, resulting in pharmacological preconditioning that protects against myocardial ischemia.

Evidence level

Class IIb, grade C.

Indication

The use of the aforementioned medications, both in cases of KD and in pediatric patients in general, is off-label.

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