e-ISSN 2527-2950
p-ISSN 2085-4145

JURNAL KEDOKTERAN DAN KESEHATAN INDONESIA

JKKI
SCIENTIA EST BASIC VITAE

Indonesian Journal of Medicine and Health

Journal homepage: https://journal.uii.ac.id/JKKI/index

VOL 12, No. 3, September - December 2021

JKKI	Volume 12	Number 3	pp 204 - 306	Jogjakarta Sept - Dec 2021	ISSN 2085-4145

Published by
Faculty of Medicine
Universitas Islam Indonesia

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The time administration and cost burden of intravenous immunoglobulin (IVIG) therapy in a 4-year-old girl with Kawasaki disease: A case report

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Case Report

ARTICLE INFO

Keywords:
Kawasaki disease,
Intravenous immunoglobulin,
IVIG,
coronary artery complication

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DOI : 10.20885/JKKI.Vol12.Iss3.art13

History:
Received: May 3, 2021
Accepted: December 25, 2021
Online: December 31, 2021

ABSTRACT

Kawasaki disease (KD) is an acute systemic vasculitis frequently affecting children under five years old. KD can cause severe complications. It can lead to coronary aneurysms in 15-25% of untreated cases. Intravenous immunoglobulin (IVIG) treatment within ten days of initial onset can reduce the rate of coronary artery aneurysms. However, IVIG administration in Indonesia is currently limited due to its high cost. The case reported a 4-year-old girl with a chief complaint of fever. She complained about a high fever seven days before hospitalization. She also complained about vomiting, cough, joint pain, diarrhea, skin peeling, and rash on her body, palms, and soles. On examination, she looked irritable and sluggish. The temperature was 39.9o C. There were red eyes without discharge, strawberry tongue, oral thrush, and red, dry, cracked lips, swollen neck lymph nodes, and skin rash on her body, palms, and soles. Laboratory testing showed microcytic hypochromic anemia with Hb 7.9 g/dL and leukocytosis 24.230/mm^3. Chest X-ray showed perihilar and paracardial infiltrates. Electrocardiogram revealed sinus tachycardia. An echocardiogram showed left ventricle dilatation with trivial mitral regurgitation and no coronary abnormalities were found. She was diagnosed with Kawasaki Disease. She was treated by IVIG 30 gr single dose during 12 hours on day 7 of initial onset, methylprednisolone injection 10 mg/8 hours, paracetamol 150 mg/8 hours, and aspirin 400 mg/8 hours orally and discharged from the hospital with improvement. There weren't any coronary artery abnormalities found. IVIG administration within ten days of initial onset in KD patients can reduce the risk of coronary artery complications. IVIG administration after day 10 of initial onset can achieve resolution of inflammation but can be insufficient for preventing coronary artery lesions (CALs).

Kawasaki Disease (KD) merupakan suatu vaskulitis sistemik akut yang sering dialami oleh anak-anak berusia di bawah 5 tahun. KD dapat menyebabkan komplikasi aneurisma arteri coroner pada 15-25% kasus yang tidak diterapi dengan baik. Terapi Imunoglobulin intravena (IVIG) dalam waktu 10 hari dari mulai onset penyakit dapat mengurangi komplikasi aneurisma arteri coroner. Akan tetapi, terapi IVIG menjadi suatu hambatan karena biaya yang mahal. Kasus ini melaporkan seorang anak perempuan berusia 4 tahun dengan keluhan utama demam. Demam dikeluhkan sejak 7 hari sebelum masuk rumah

sakit. Pasien juga mengeluh muntah, batuk, nyeri sendi, diare, kulit mengelupas, dan timbul ruam kemerahan di badan, telapak tangan, dan kaki. Pemeriksaan fisik didapatkan pasien tampak rewel dan lemas dengan suhu 39.9 o C. Mata tampak merah tanpa disertai discharge, lidah tampak kemerahan, sariawan, bibir kering dan pecah-pecah, pembesaran kelenjar getah bening leher, dan ruam kemerahan di tubuh, telapak tangan, dan kaki. Pemeriksaan laboratorium menunjukkan anemia mikrositik hipokromik dengan Hb 7,9 g/dL dan lekositosis 24.230/mm3. Foto thoraks tampak gambaran infiltrat perihilar dan paracardial. Elektrokargiogram menggambarkan sinus takikardi. Echokardiogram tampak dilatasi ventrikel kiri dengan regurgitasi mitral trivial tanpa disertai kelainan arteri koroner. Pasien didiagnosis Kawasaki Disease. Pasien mendapat terapi IVIG 30 gr dosis tunggal selama 12 jam di hari ke-7 demam, injeksi metilprednisolon 10 mg/8 jam, parasetamol 150 mg/8 jam, dan aspirin 400 mg/8 jam. Pasien dapat dipulangkan dari rumah sakit setelah tujuh hari perawatan dengan perbaikan. Pasien tidak mengalami komplikasi arteri koroner. Pemberian IVIG pada pasien KD dalam 10 hari awal terjadinya penyakit dapat mengurangi risiko terjadinya komplikasi pada arteri koroner. Terapi IVIG setelah 10 hari dapat memperbaiki inflamasi tetapi tidak cukup mencegah terjadinya komplikasi arteri koroner.

INTRODUCTION

Kawasaki disease (KD) is afebrile, acute systemic vasculitis frequently affecting children under five years old.[1] Etiology of KD remains unknown, with the incidence varies according to geographic area. The highest incidence is in Japanese descendant children with a rate of 330.2 per 100.000 in 2015.[2] According to ethnic variation, Asians and Pacific Islanders have the highest rates with 30.3 per 100.000 children under five years old.[2,3] In Indonesia, there are an estimated 5000 cases per year, yet the cases that can be diagnosed are less than 200 cases per year.[4]

Kawasaki disease can cause severe complications. It can lead to acquired heart disorder in febrile children, especially in the coronary arteries.[1,5] Coronary complications such as coronary aneurysms can affect 15-25% of untreated cases. It can cause myocardial infarction, sudden death, or ischemic heart disease.[5] Prompt treatment with intravenous immunoglobulin (IVIG) can reduce the rate of coronary artery aneurysms from 25% to 4%.[1] Unfortunately, it becomes challenging because IVIG treatment is costly. Moreover, the signs and symptoms of KD mimic other acute febrile illnesses. So, early identification and prompt treatment should be made to avoid more severe complications.

CASE DESCRIPTION

A 4-year-old girl was brought by her parents to the hospital with a chief complaint of fever. In the past seven days before hospitalization, she complained about high fever throughout the day. Fever could relieve by consuming febrifuge, but her body temperature still increased after several hours. She also complained about vomiting and cough. Her parents brought her to the doctor, and he gave her some medicines. Unfortunately, the symptoms still existed. Three days later, a rash appeared on her body, palms, and soles without the itch. The fever had not relieved. She also complained about slight breathlessness. There were red eyes without eye discharge and red, dry, and cracked lips. Her tongue becomes reddish. She looked irritable, sluggish, and dehydrated. Then, her parents took her to the hospital. The doctor advised her to be hospitalized. During hospitalization, she was still fever. The joint pain, diarrhea, and skin peeling, especially on her hands, also occurred. We report that previously, the patient didn't have the same medical history. Similar disease within the family was not found in this patient. She was born in a midwifery clinic by vaginal delivery. All primary immunizations have also been carried out as per the schedule. She was breastfed until two years old, and all the developmental milestones showed normal. Her father is a farmer, and her mother is a housewife. She doesn't have national health insurance (Badan Penyelenggara Jaminan Sosial/ BPJS). He lives with her parents, brother, grandparents, and aunt.

On physical examination, general conditions were conscious, spontaneous breathing, and no

retraction. She looked sluggish and irritable. All the vital signs were stable, but the temperature was 39.9° C. Her weight was 15 Kg, and her height was 97 cm. Nutritional status was normal. There was redness in her eyes, lips fissure, oral thrush, swollen and red tongue, swollen of neck lymph nodes, skin peeling, and skin rash on her body, palms, and soles. There wasn't chest retraction. Other physical examinations showed normal findings.

Laboratory testing showed microcytic hypochromic anemia with Hb 7.9 g/dL, MCV 67.8 Fl, MCH 21.9 pg/cell, MCHC 32.4 %, and leukocytosis with leukocyte 24.230 /mm^3. Differential cell count showed Bas/Eos/Bat/Seg/Lim/Mon: 0.1/0.1 (low)/2.5 (low)/73.6 (high)/20.0 (low)/3.7. Then, she was checked for peripheral blood testing to find out the cause of anemia. The result showed mild anisocytosis (microcytic), mild poikilocytosis (ovalocyte, elliptocyte, teardrop), neutrophilia, and vacuolization. Urine testing was unremarkable. Chest X-ray showed perihilar and paracardial infiltrates and no heart enlargement. Electrocardiogram revealed sinus tachycardia. An echocardiogram showed left ventricle dilatation with trivial mitral regurgitation, and no coronary abnormalities were found.

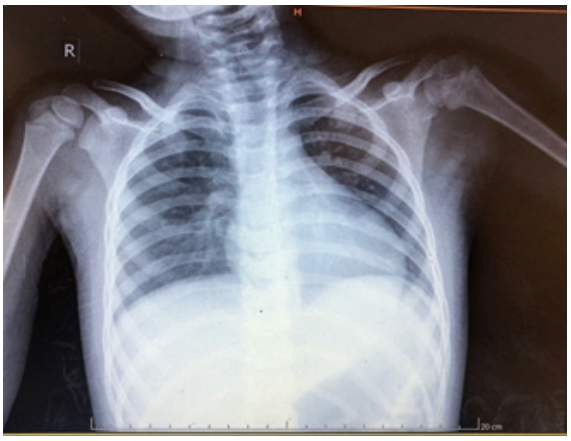

Figure 1. Chest X-ray feature of the patient

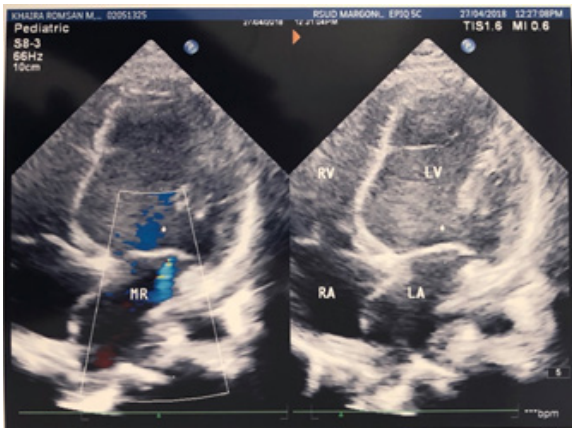

Figure 2. Echocardiogram of the Patient

She was hospitalized in the pediatric ward and diagnosed with Kawasaki Disease. She was treated by antibiotic injection of ampicillin injection 500 mg/6 hours and gentamicin injection 37.5 mg/12 hours, Intravenous Immunoglobulin (IVIG) 30 gr single dose intravenously in day 7th of initial onset, methylprednisolone injection 10 mg/8 hours, paracetamol 150 mg/6-8 hours

for relieving febrile, aspirin 400 mg/8 hours per oral, captopril 5 mg/12 hours, furosemide 10 mg/12 hours, and emollient for dry, cracked lips during hospitalization.

On the second day's follow-up of hospitalization, the symptoms of red eyes, joint pain, thrush, swollen and red tongue, swollen neck lymph nodes, skin peeling, and skin rash on her body, palms, and soles still existed. Still, fever and dry, cracked lips were gradually improving. On the 3rd day, red eyes improved, but other symptoms haven't been relieved. On the 4th day, skin rash was relieved. Lip fissure and oral got an improvement on the 5th day. She could eat well on the 6th day. She was discharged from the hospital with improvement. There were not any severe complications such as coronary artery abnormalities found in this patient.

Data were taken from the patient's history, clinical findings, and medical records. The parents had given their consent to take some lessons from the case for study purposes. The case received ethical approval from the Faculty of Medicine, Universitas Jenderal Soedirman (reference no.: 198/KEPK/IX/2021).

DISCUSSION

Clinical criteria were used to diagnosis KD.[1] According to the American Heart Association (AHA), the diagnosis of classic or complete KD is established if the patient suffered from prolonged fever > 5 days that fulfill 4 of the five clinical criteria for KD include (1) mucosal changes: erythema and cracking of lips, "Strawberry tongue" erythema, and prominent fungiform papillae and erythema of the oral and pharyngeal mucosa, (2) conjunctivitis: bilateral bulbar non-exudative conjunctival injection, often limbic sparing, (3) polymorphous rash: maculopapular diffuse erythroderma or erythema multiforme-like. Less commonly, urticarial or fine micro-pustular eruptions, (4) extremity changes. Clinical features are erythema and edema of the hands and feet in acute phase, periungual desquamation and subacute phase. The last criteraia are (5) Lymphadenopathy (acute, non-suppurative, cervical lymphadenopathy, ≥ 1.5 cm diameter), typically unilateral.[1,2,6,7] There are several nonspecific clinical manifestations in addition to diagnostic criteria of KD, including irritability, uveitis, cough, vomiting, diarrhea, abdominal pain, arthralgia, arthritis, abdominal pain, aseptic meningitis, hypoalbuminemia, liver function disorder, gall bladder hydrops, and heart failure.[6] The patients who don't meet the complete diagnostic criteria for KD are classified as incomplete or atypical KD.[1,2] Incomplete or atypical KD diagnosis should be considered if there are prolonged fever, less than 4 of the clinical diagnostic criteria, and suitable with laboratory or echocardiographic results.[1] In our case, the patient suffered from fever for seven days before hospitalization. It is accompanied by lips fissure and strawberry tongue appearance, bilateral non-purulent conjunctivitis, dysmorphic skin rash, palmar and plantar erythema, skin peeling, and cervical lymphadenopathy. The additional complaints in this patient were irritability, cough, vomiting, and diarrhea. She fulfilled all of the diagnostic criteria for classic or complete KD. So, she was diagnosed with complete KD.

There are three clinical phases of KD: acute febrile phase, subacute phase, and convalescent-phase. The acute hot phase usually lasts 1–2 weeks. The subacute phase occurs about 10 to 25 days after the onset of fever, after resolution of fever, rash, and lymphadenopathy. The convalescent phase begins after the resolution of the clinical signs of KD.[8] The patient was brought by parents in the acute febrile phase of KD.

Supplementary laboratory criteria supporting KD diagnosis are albumin level < 3 mg, CRP > 3 mg, erythrocyte sedimentation rate (ESR) >40 mm/h, elevated alanine aminotransferase, leukocytosis (white cell count >15.000/mm), normochromic, normocytic anemia for age, and sterile pyuria (>10 white blood cell/mm3).[9]

Laboratory testing in this patient showed microcytic hypochromic anemia with Hb 7.9 g/dL, MCV 67.8 Fl, MCH 21.9 pg/cell, MCHC 32.4 %, and leukocytosis with leukocyte 24.230 /mm^3. A study conducted by Tsai C-M et al. identified three parameters related to hemoglobin (Hb,

MCH, MCHC) that decrease in KD.[10] Hepcidin encoded by the hepcidin antimicrobial peptide (HAMP) gene is an element of the inflammation-associated anemia mechanism. HAMP promoter hypomethylation promotes hepcidin expression in KD patients. The hepcidin upregulation can lead to transient anemia and hypoferremia in the acute inflammatory phase of KD. This correspond with lower Hb, MCH, and MCHC in patients with KD.[10] Tsai C-M, et al. studied a novel score system of blood tests for differentiating Kawasaki Disease from febrile patient. The study reported that there were eight dependent predictors of blood tests score, including platelets, eosinophil, alanine aminotransferase, CRP, Hb, MCH, MCHC and monocyte. According to that study, the total score system of a blood test of 14 constitutes the best sensitivity and specificity prediction rate for differentiating Kawasaki disease from other febrile children.[10]

Chest X-ray in this patient showed perihilar and paracardial infiltrates and no heart enlargement. A study conducted by Advani that evaluated a chest X-ray of 503 KD patients at the acute stage showed that almost all KD patients revealed pulmonary infiltrates. 67% of patients showed enters in bilateral lung areas, especially in perihilar and paracardial regions. It can be inferred that pulmonary infiltrates can support the diagnosis of KD, especially in unlikely cases of incomplete KD.[11] Otherwise, it is different from the study Umezawa et al. There were 14.7% KD patients with chest X-ray abnormalities. This might be because subjects included in that study were only patients with complete KD.[12] Picazo et al. reported that radiologic findings in KD patients are uncommon. Their study showed that chest X-ray abnormalities were occurred in 5 (20.8%) of 24 cases, in the acute febrile phase, because of the lower respiratory tract inflammation or cardiac insufficiency.[13]

An Electrocardiogram of this patient revealed sinus tachycardia. An echocardiogram showed left ventricle dilatation with trivial mitral regurgitation and no regional wall motion abnormality (RWMA). Fortunately, no coronary artery aneurysm was found. According to the study, coronary artery dilatation can be found after the 6th day of the initial event, but generally, its peak can be achieved between 2-6 weeks after onset.[5] Fever duration more than seven days and hypoalbuminemia can be predictive factors for coronary artery dilatation in KD patients.[5]

The patient was treated by antibiotic injection of ampicillin injection 500 mg/6 hours and gentamicin injection 37.5 mg/12 hours, IVIG 30 gr single dose intravenously in day 7 of initial onset, methylprednisolone injection 10 mg/8 hours, paracetamol 150 mg/6-8 hours for relieving febrile, aspirin 300 mg/6 hours per oral, captopril 5 mg/12 hours, and furosemide 10 mg/12 hours. The targeted therapy in the acute phase of KD is to decrease inflammation and arterial disorder and avoid thrombocytosis if there are coronary artery abnormalities.[1]

The primary therapy for KD patients is IVIG.[1] IVIG is usually given to medicate rheumatologic and autoimmune disorders. Several mechanisms have been proposed to elaborate the IVIG effect as anti-inflammation. These elevate autoantibodies clearance through competitive binding of neonatal Fc receptors (FcRn), inhibitory Fc receptor FccRIIB activation on macrophages, and adhesion molecules blockade.[14] Peripheral blood lymphocytes in KD patients showed elevated proliferative and decreased apoptotic responses. IVIG treatment was reported to have a pro-apoptotic effect. FAS may mediate this since IVIG contains anti-FAS antibodies.[14] In the acute phase, KD patients have lower Treg numbers. IVIG can affect the number and function of regulatory T cells (Tregs) in KD patients that control inflammation.[14]

The timing for giving the treatment is important for attaining the best outcome.[1,14,15] IVIG treatment in the acute phase of KD can reduce the incidence of coronary abnormalities. IVIG should be administered within the first ten days of fever onset when the diagnosis of KD is established to prevent coronary complications.[1,14-16] IVIG treatment before day 5 of initial onset seems no more likely to prevent cardiac complications than treatment on days 5-9. It might be associated with an increased

need for IVIG retreatment.[6] The recommended dose is 2 gr/kg as a single infusion during 12 hours, together with aspirin (ASA), especially in the first ten days of illness.[1,6,14]

IVIG and ASA administration can reduce the incidence of coronary artery lesions (CAL) in KD patients.[1,2,16] The incidence of CAL decreases from 25 to 4% after the treatment.[16] ASA can be provided to KD patients during the acute phase of illness with 80 to 100 mg/kg/day doses in four doses with IVIG.6 ASA has anti-inflammatory effect at high dose (80 to 100 mg/kg/day) and antiplatelet activity at low dose (30 to 50 mg/kg/day). It can't reduce the progression of coronary complications.[1] In our case, the patient, was administered by IVIG 30 gr single dose during 12 hours of infusion as early as she was diagnosed with KD. She also got ASA 300 mg/6 hours together with IVIG.

Initial treatment with IVIG and ASA is recommended for 1) Both complete and incomplete KD patients within ten days of fever onset, 2) KD patients after ten days of illness onset if there are persistent unexplained and coronary artery abnormalities along with CRP or ESR elevation that imply ongoing systemic inflammation, 3) administration of moderate to high dose ASA is acceptable until fever get improvement, even though ASA can't afford to decrease coronary artery aneurysms, 4) IVIG should not be given to KD patients after 10th day of illness onset without fever, a significant increase of inflammatory markers, or coronary artery abnormalities, 5) High ESR alone that persists after IVIG therapy should not be assumed as a sign of IVIG resistance.[1]

The AHA recommends IVIG administration to KD patients within ten days of initial onset.[6,8] The coronary artery changes usually begin on days 7 to 10. KD treatment within ten days, especially within seven days of illness onset, is optimal. The efficacy of treating IVIG after ten days of start has not been clarified.[17] IVIG treatment after day 10 of the illness is considered if KD patients show persistent fever or aneurysms and evidence of systemic inflammation with increased ESR or CRP, even though the potential effect of delayed IVIG treatment remains uncertain.[6,8,15] A study by Muta et al. evaluated the effectiveness of IVIG treatment of KD after day 10 of initial onset. After ten days of illness, it was reported that IVIG administration could resolve the inflammation but is insufficient for preventing coronary artery lesions (CALs). [17]

A study by Bal et al. revealed that IVIG administration within ten days of illness onset is essential to reduce the risk of cardiac abnormalities. The age of less than one year and high ESR should be considered for delayed improvement of coronary artery (CA) lesions in children with KD.[15] In this case, the patient responds to the treatment after IVIG administration on day 7 of initial onset.

However, even though IVIG has improved KD outcomes and decreased the incidence of CALs, IVIG administration in Indonesia is currently limited due to its high cost. The cost burden for IVIG therapy often exceeded the parent's ability. IVIG treatment is expensive for low and middle-income families, especially those who don't have any insurance.[18] In our case, IVIG therapy administered to the patient was 30 gr. A vial of 5% IVIG contains 50 ml IVIG, which equals 2.5 gr IVIG in each vial. The cost of 1 vial of 5 % IVIG is Rp. 2.160.000 (according to the national e-catalog). It meant that the patient needed 12 vials for 30 gr IVIG. The total cost spent on IVIG treatment in this patient reached Rp. 25.920.000. It became a cost burden for the patient without any insurance. Unfortunately, the parents paid for all the costs of IVIG treatment because they didn't have any national insurance. Yet, estimation of total expenses for follow-up and treatment in KD patients treated by IVIG results in a lower price and better outcomes when it's compared to KD patients without IVIG therapy.[19]

Few studies evaluated cost burden and cost-effectiveness in KD patients treated by IVIG. In contrast, in Indonesia, no studies compared the cost-effectiveness or cost burden of treating Kawasaki Disease in children using IVIG compared to those without IVIG therapy. A study in Thailand evaluated the long-term cost-benefit of IVIG treatment in children with

KD. It reached long-term follow-up (10-21 years) of the total cost for managing KD patients with and without IVIG treatment. Reduction of CAA from 25 percent to 4 percent with IVIG treatment was assumed based on previously published data. Cost-per-effectiveness analysis showed more effectiveness in the IVIG treatment group (359.576 baht vs. 383.614 baht). Net cost analysis similarly demonstrated lower costs in the IVIG treatment group (25.365.215-baht vs. 33.451.129 baht). Estimation of total expenses for follow-up and treatment for a healthy life (until 60 years old) was more expensive in the non-IVIG treatment than the IVIG treated group (75.482.803 baht vs. 29.883.833 baht). The study concludes that treatment of all KD cases in Thailand with IVIG is likely to result in lower costs and better outcomes when compared to no treatment with the IVIG policy.[19]

A recent study by He et al. assessed the efficacy of IVIG regimens in KD patients to find more cost-effective therapy options. The study compared IVIG administration with doses of 2 g/kg once, 1 gr/kg for two consecutive days, and 1 gr/kg once. It showed that a single dose of 1g/kg IVIG is a low-cost treatment with the same efficacy as 2 g/kg IVIG and can be an option for the initial therapy of KD patients.[18]

In our case, the patient also received methylprednisolone injection therapy. Previously, corticosteroids, as anti-inflammatory agents, were used before IVIG became standard therapy. But, corticosteroids can't afford to become monotherapy for KD patients because it was reported to lead to the progressivity of CALs. Corticosteroids can be added to standard IVIG therapy to avoid IVIG resistance in KD. It can inhibit the release of high-mobility group box-1 (HMGB1) and Interleukin (IL)-1α, which may have a role in IVIG resistance in KD.20 A study by Wardle showed that steroid use in the acute phase of KD could reduce coronary artery aneurysms, shorten the length of hospitalization, and reduce the infinity of clinical symptoms. It can also decrease the level of inflammatory marker (CRP, ESR).[21]

The strength case management of this KD patient is IVIG administration on day 7 of initial onset just after the diagnosis was established. It's essential to reduce severe coronary artery complications. IVIG treatment, in this case, can prevent coronary artery complications. An echocardiogram showed no coronary artery aneurysms found. IVIG administration in Indonesia is currently limited due to its high cost. Fortunately, the patient received IVIG treatment as early as possible. We didn't examine other inflammatory markers, such as CRP, because of cost consideration. The cost burden for IVIG therapy has been exceeded the parent's ability. Furthermore, the patient didn't have any national insurance. However, we can establish a diagnosis of KD according to the AHA criteria of KD, especially in a limited setting.

CONCLUSION

Kawasaki disease can cause serious complications, especially coronary artery aneurisms. IVIG should be administered, especially within ten days after the initial onset of illness when the diagnosis was established to prevent sequela. After day 10 of the initial start, IVIG administration can resolve inflammation but is insufficient for avoiding CALs. IVIG treatment becomes challenging because it's costly. Yet, it results in lower cost and better outcomes compared to KD patients without IVIG therapy.

CONFLICT OF INTEREST

There was no conflict of interest in this manuscript.

ACKNOWLEDGEMENT

We would like to thank Prof. Dr. Margono Soekarjo General Hospital that has supported the patient during hospitalization. The authors didn't receive any grants from profit or non-profit funding institutions.

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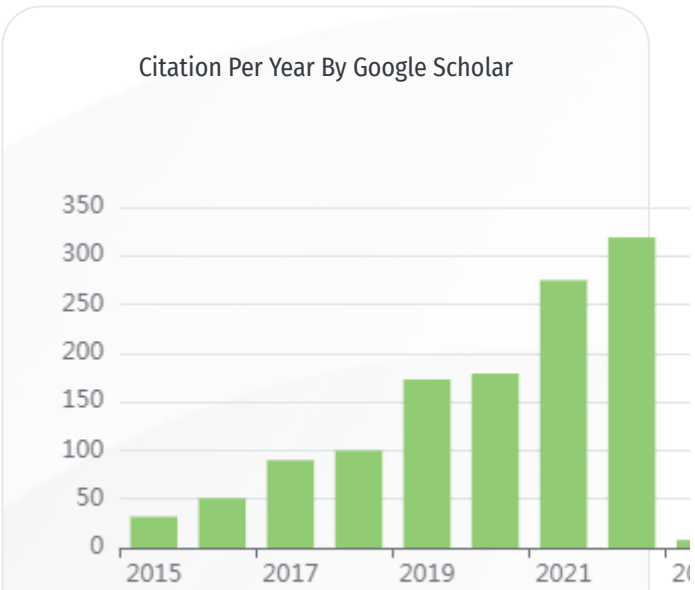

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