CASE REPORT ON KAWASAKI PATIENT WITH IMMUNOGLOBULIN NON-RESPONSE SUCCESSFULLY TREATED WITH INFLIXIMAB

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ABSTRACT

Background: Kawasaki disease KD is self-limiting acute multi-systemic vasculitis of unknown etiology. Current treatment recommendations for acute KD include IVIG and aspirin, but there are no evidence-based guidelines for children who do not respond to IVIG treatment. Over the past few years, increasing knowledge of the pathophysiology of KD has resulted in the identification of key inflammation mediators and the use of biologic pathway targeting agents such as TNF and IL-1 inhibitors for children with IVIG-resistant disease.

Case presentation: A 11-month-old girl was diagnosed with typical KD and treated with 3 IVIG and 1 corticoid therapy, but the coronary arteries continued to dilate. After that, the patient was treated successfully with Infliximab.

Keywords: Kawasaki disease, IVIG resistance, Infliximab

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I. INTRODUCTION:

Kawasaki disease KD is self-limiting acute multi-systemic vasculitis, the most common cause of acquired heart disease in children under 5 years old. The disease has 6 typical symptoms: fever > 5 days, skin rash, swelling or erythema of the hands or feet, inflammation of the oral cavity, conjunctivitis without excretion of inflammatory fluid, neck lymph nodes. Epidemiological studies and clinical observations suggested that infection may be a trigger, but so far the etiology has been still inconsistent.

In the early phases of inflammatory reaction, polymorphonuclear neutrophils and macrophages release proinflammatory cytokines: IL-1β, TNFα, IFNγ. In which IL-1β, TNFα are related to vascular endothelial cell destruction and coronary artery (CA) damage in the acute phase of the disease.

So far, recommendations for treating Kawasaki disease in the acute phase have been still IVIG and aspirin. The use of IVIG in treatment has reduced the risk of coronary aneurysm damage from 25% to 5%. However, about 15-20% of children did not respond to basic treatment and the disease continued to progress, having a fever again after the first dose of IVIG - this group of children is at high risk of coronary artery damage. Factors such as male sex, elevated CRP, severe anemia, low albumin, low Na are used to predict the severity of the disease and the risk of IVIG resistance.

The increase in levels of IL-1β and TNFα in the acute phase of the disease shows the role of these two pro-inflammatory cytokines in the systemic inflammatory reaction and coronary artery damage in Kawasaki disease, creating a new direction in IVIG treatment with the target cell drugs. [1]

II. CASE PRESENTATION

- Two days after discharge (Day 19 of the disease), the child had a fever again of 38.4 degrees Celsius, flaked hands and feet, eyes were red, lips were reddish, blood tests showed leukocyte of 39 G/L, CRP 82 mg/dl, Procalcitonin 0.026, TC 987 G/L, echocardiography (Day 20) showed the bilateral coronary arteries continued to dilate (RCA 3.3-4.5mm, LmCA 4.4mm, LAD 3.8-4.1mm) -> Diagnosis: IVIG-resistant Kawasaki.

The 11-month female patient was admitted to the hospital because of fever and red eyes on the second day. The disease took place 23 days before admission:

- On the sixth day (Day 6) of the disease, the child had full 6/6 typical symptoms of Kawasaki disease, blood tests showed elevated CRP (300mg/dl). The child was diagnosed with typical Kawasaki disease, treated according to the regimen with IVIG (2g/kg) and aspirin 50mg/kg on Day 6 of the disease. After IVIG infusion, the child still had a fever of 38.5-39 degrees Celsius, red eyes, red lips, skin erythema lost; echocardiography on day 8 showed the bilateral coronary arteries not dilated (RCA 2.5-1.7mm, LmCA 2.7mm, LCx: 1.5mm, LAD 1.9mm). The child was treated with Methylprednisolon (30mg/kg/day) for 3 consecutive days from Day 9-Day 12. After infusion, the child had no fever, started flaking her hands, eyes and lips were not red; echocardiography on day 12 showed the coronary arteries within the upper limit of normal level. The patient was discharged and continued to receive maintenance treatment with oral prednisolon at a dose of 2mg/kg/day.

- However, after 2 days of discharge (Day 14 of the disease), the child had a fever again of 38.5 degrees Celsius, flaked fingers, toes, blood tests showed increased leukocyte, CRP 40 -> 80 mg/dl, echocardiography on day 14 showed the bilateral coronary arteries dilated (RCA 2.9mm, LmCA 3.5mm, LAD 2.7mm) -> Diagnosis: IVIG-resistant Kawasaki. The child was treated with IVIG for the second time at a dose of 2g/kg on day 14 of the disease. After infusion, the child had no fever; tests showed that leukocyte decreased, CRP 80 -> 11 mg/dl. Echocardiography (day 17) showed the bilateral coronary arteries continued to dilate (RCA 2.9-3.6 mm, LmCA 3.5mm, LAD 2.7mm). The child was discharged and treated with Prednisolon and Aspecig (5mg/kg/day).

- After IVIG infusion, the child still had a fever of 40-41 degrees Celsius, red eyes, red lips; echocardiography (day 21) showed the bilateral coronary arteries continued to dilate -> Diagnosis: IVIG-resistant Kawasaki -> Transfer to National Children’s Hospital.

- Tests on the 23rd day of the disease
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• BC: 20.4 G/l, Neutrophil 82.5%, Platelet 930 000, Hb 98 g/dl
• Coagulation: PT 105%, APTT 28s, Fib 6.75, D-dimer 1960
• Infection: CRP 162, Pro-calcitonin 0.073
• GOT/GPT: 42/47.6, pro-BNP: 14.93, ferritin 115.2, triglycerid 0.78
• CD3: 1292, CD4 718, CD8 515 (↓)
• Blood culture, urine, total urine analysis: negative
• CMV, EBV: Negative

Diagnosis: IVIG-resistant Kawasaki, coronary arteries continued to tend to dilute.

Question posed: What is the next treatment for this patient to prevent coronary arteries from continuing to dilute?

Treatment: The patient was interdisciplinarily diagnosed and decided to treat with Infliximab at a dose of 5mg/kg for 2 hours (Day 23 of the disease)

Progression of disease after infusion of Infliximab (IFX)
• Immediately after the end of IFX infusion, the child had a fever of 38.5 degrees Celsius.
• Follow-up continued immediately after infusion, the child had no fever completely, no symptoms of Kawasaki disease, tests showed that leukocyte decreased, CRP decreased, platelet decreased shown by chart 1.
• Echocardiography after IFX infusion showed the coronary arteries not diluted (RCA 5.1mm, LmCA 3.9mm, LAD 5.1mm, Lcx 3.1mm)

Chart 1: Evolution of CRP, platelet and treatment process of patient

• Started using Wafarin from Day 33 of the disease.
• The patient was discharged on the 37th day of the disease, maintaining the use of anticoagulant Wafarin with INR 2.1, combining Aspigin 3mg/kg/day.

III. DISCUSSION

Kawasaki is the acute fever with systemic vasculitis first described by Tomisaku Kawasaki in 1961 with the name "skin and mucosa syndrome with swollen lymph nodes and characteristic scalp flaking in children". The disease causes damage to many areas, especially coronary arteries, becoming a major cause of acquired heart disease in children in developed countries. Follow Kawasaki update regimen by the 2017 AHA, with patients diagnosed with Kawasaki were treated with IVIG as soon as possible in the first 10 days of the disease from onset of fever, at a dose of 2g/kg intravenously-infused in 10-12 hours and taking high-dose aspirin with anti-inflammatory effect, at a dose depending on the regimen. However, approximately 15-20% of patients had a fever again or a fever lasting at least 36 hours after the end of IVIG infusion called IVIG-resistance. For patients treated with IVIG at high doses for the first 10 days of the disease, 20% of patients continued to have bilateral coronary arteries diluted in the near-
transverse segment, 5% of patients continued to progress to coronary artery aneurysms (≥ 6 mm) and 1% of patients continued to progress to giant coronary artery aneurysms (≥ 8mm) [2]. Our patients were in 5% of patients who continued to progress to coronary artery aneurysms. So the question is whether treated with IVIG at high doses as recommended by most cardiovascular associations and international consensus, the patient’s coronary arteries continued to dilate and develop coronary artery aneurysms, how are prognosis and treatment?

With today's scientific and technological advances, medicine is increasingly going into the molecular mechanism causing disease and developing targeted drugs.

When studying changes in inflammatory factors in Kawasaki disease, study by Shereya A. in 2017 showed an increase in many pro-inflammatory factors such as IL-1, IL-6, IL-20, IFN-γ, TNF-α ... and a decrease in anti-inflammatory factors such as IL-10, TGF-β, NKG2D...leading to inflammation and destruction of blood endothelium [3].

Similarly, study by Florence A. also showed that in Kawasaki's pathogenesis, both specific and nonspecific immune systems involved. During acute inflammation, polymorphonuclear neutrophils and macrophages during acute inflammation released inflammatory cytokines: IL-1β, TNF-α, IFN-γ ... in which IL-1β, TNF-α were related to endothelial destruction and coronary artery damage in the acute phase of Kawasaki disease. TNF-α is a pro-inflammatory cytokine produced primarily by activated macrophages, a few by T cells and prickle cells; in addition, TNF-α also increases a number of other important pro-inflammatory cytokines such as IL-6 causes activation of T lymphocytes, anticoagulant factors cause thrombocythemia. The inflammatory process in the vascular wall further activates the leukocyte chemical dynamics to the vascular wall (especially coronary arteries), increasing the number of TNF-α and the number of TNF-α receptors (this phenomenon has been described in Kawasaki disease patients with coronary artery aneurysms). Some recent studies showed that there was no difference in the concentration of TNF-α before IVIG treatment in both groups with or without coronary artery damage. However, after IVIG treatment, TNF-α concentration was significantly higher in the group that did not respond to IVIG and had coronary artery damage, decreased in the group that had no coronary artery damage. Interestingly, when using TNF-α inhibitors or TNF-α receptor blockers, local inflammation and coronary artery wall destruction were improved.

This is the basis of the use of targeted drugs in the treatment of Kawasaki against TNF-α. In addition, TNF-α also increases some proteins in which MMPs is an enzyme that acts to lyse proteins causing destruction of collagen and elastin layers of the arterial wall. In particular, MMP9 plays a signaling role of TNF-α and plays a role in the coronary artery aneurysm mechanism of Kawasaki disease because MMP9 is found in the coronary artery aneurysm position and also in the position where the coronary artery is not damaged. Studies showed that eliminating this protein will reduce coronary artery damage although the inflammatory process continues to progress [1].

Therefore, agents that can inhibit the activity of TNF-α, inhibit the activity of MMP protein (e.g., ulinastatin - inhibits lysis of polymorphonuclear neutrophils, doxycycline - antibiotic with effect to inhibit MMP protein function), effective in the treatment to prevent coronary artery aneurysms in preclinical testing - are promising treatments in children with Kawasaki disease [1].

In fact, according to the 2017 regimen by AHA with IVIG transfusion resistance cases, Infliximab was the first monoclonal anti-TNF-α antibody used to treat children at a dose of 5mg/kg slow intravenous infused in 2 hours with a speed according to the manufacturer's instructions, in addition to traditional treatment options such as: second dose of IVIG, second dose of IVIG + corticoid. In addition, alternatives are anakinra, cyclosporine, cyclophosphamide, plasma filter with different levels of evidence. After IFX treatment, decreased concentrations of pro-inflammatory cytokines led to a decrease in systemic inflammation, but vasculitis markers such as VEGF (Vascular Endothelial Growth Factor) and S100 still increased so they did not completely prevent vasculitis [2].

A number of clinical case reports and clinical trials with a sample size of about 15-198 patients with an average age of 23 months - 4.6 years old and varied study designs gave the following results: after one dose of IFX, most IVIG-resistant patients decreased
fever duration, decreased duration of hospital stay, decreased inflammatory reactions in the acute phase, effective and well-tolerated; however, 2012 study by Mori et al. showed that 2/20 (10%) of IFX-resistant patients had plasma replacement, 19/20 (95%) of patients had coronary artery damage regressed, 1/20 (5%) of patients appeared coronary artery damage at 30 days after onset of disease and had it completely regressed after 1 year [4] [5] [6].

In order to predict the risk of IVIG resistance among patients with Kawasaki based on clinical symptoms and initial tests prior to treatment to identify patients who do not respond to IVIG and need additional treatment soon to decrease the risk of coronary artery damage, many prognostic studies of the risk of IVIG resistance in Kawasaki patients have been conducted for many years. The study by Kobayashi T. et al. [7] was conducted on 750 children of an average age of 29 months diagnosed with Kawasaki, started treatment at 4.0 ± 1.5 days of disease with 21% of patients who did not respond to IVIG and 5-8% of patients who had coronary artery damage. The comparison between two Kawasaki groups that responded and did not respond to IVIG showed that in the group that did not respond to IVIG, there was a higher rate of polymorphonuclear neutrophils in AST, ALT, CRP, statistically significant lower blood concentrations of Na and Chlorine than the group that responded to IVIG (p < 0.001). Using multivariate regression analysis method provides 7 prognostic factors of IVIG resistance including: Na ≤ 133, AST ≥ 100, CRP ≥ 100, platelet ≤ 30 x 10, rate of polymorphonuclear neutrophils ≥ 80%, age ≤ 12 months, IVIG treatment before 5 days of disease.

IV. CONCLUSION

This is the first case where we used anti-TNF-Infliximab drug in the treatment of IVIG-resistant Kawasaki with coronary arteries continued to dilute in the 23rd day of the disease. This opens up a new direction - the targeted drug in the treatment of IVIG-resistant Kawasaki in Vietnam when we have a deeper understanding of the pathogenesis of Kawasaki disease. Factors for prognosis of IVIG-resistant Kawasaki should also be assessed at the time of admission to early predict the patient's risk of IVIG resistance and coronary artery damage. From this clinical case, should we use IFX sooner for IVIG-resistant Kawasaki patients?

REFERENCES