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Case Report

Etanercept as Rescue Therapy for Refractory Kawasaki Disease

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Abstract

Kawasaki disease is a febrile vasculitis occurring in infants and children treated with first line intravenous immunoglobulin (IVIG) and aspirin. However unresponsiveness to IVIG is not rare. This case report illustrates a girl with Kawasaki disease with fever persisting through two doses of IVIG and methylprednisolone and her fever was subsided only after using etanercept, a tumor necrosis factor-α antagonist.

Keywords: Kawasaki disease; Etanercept; IVIG

Introduction

Kawasaki disease (KD) is a multisystem febrile vasculitis more commonly found in children of Asian descent. Classic KD presents as persisting fevers with oral mucositis, bilateral non-exudative conjunctivitis, cervical lymphadenopathy, swelling and desquamation of the peripheral limbs and a widespread polymorphous rash. The main complication of KD is coronary aneurysm formation, ultimately resulting in coronary artery disease (CAD). In developed nations, it is the leading cause of acquired CAD in children below the age of 5 [1]. Taiwan has a high incidence of KD, with 67.3 cases per 100,000 below the age of 5 [2]. Although the American Association of Pediatrics (AAP) and the American Heart Association (AHA) recommend intravenous immunoglobulin (IVIG) with high-dose aspirin as the mainstay treatment for children with KD [1], we found in a recent study published in 2010 that 15.3% of KD patients in our hospital are resistant to IVIG [3]. This rate of IVIG resistance is comparable to larger studies which show that IVIG resistance may occur in up to 20% of patients [4]. Newer therapies are therefore required for these refractory cases. The off-label use of tumor necrosis factor-α (TNF-α) antagonists has been shown to be promising in refractory KD, but not yet proven [5].

The patient in this case report presented with refractory KD; her fever failed to resolve despite two doses of IVIG and pulse methylprednisolone. Her fever subsided only after the use of etanercept. This will be the first known reported case of KD in Taiwan effectively treated with etanercept.

The Case

Admission

A previously well 20-month-old Taiwanese girl, weighing 13kg, presented to a tertiary hospital with a 5 day history of high-grade fevers (peaking at 39.7°C). Associated symptoms of bilateral conjunctival injection, a strawberry tongue, lip erythema, and a polymorphous rash over hands, feet and back were noted. At this time, she also presented with vomiting and decreased urine output, as well as a cough and decreased appetite and activity.

Laboratory data at the time of her admission (day 5 of fever), revealed high white blood cell (WBC) count (12.1 × 1000/uL), elevated band count (40%), neutrophil (35.0%), elevated C-reactive protein (CRP) (305.82mg/L), elevated erythrocyte sedimentation rate (ESR) (66mm/hr), normal platelet count (Plt) (211 x 1000/uL) deranged liver function enzymes (glutamic-pyruvic transaminase 170IU/L), and normocytic anaemia (haemoglobin 9.3g/dL).Initial 2-D echocardiography was performed on day 6 after disease onset, and showed a RCA diameter of 1.9mm, and a LCA diameter of 3.4mm. According to institutional practice, coronary artery dilatation was defined as any coronary artery diameter of more than 3mm in a patient less than 5 years old, a definition which adheres to the Japan Ministry of Health Guidelines [6].

Given the patient's classic presentation, the diagnosis of KD was confirmed. Accordingly, high dose aspirin was administered, with IVIG 2g/kg given on the second day of admission (day 6 of fever). She was also commenced on IV cefotaxime in the possible event of an infectious cause.

On day 7 of her illness, the patient experienced a hypotensive episode of BP 82/38mmHg. Laboratory data revealed hypoalbuminemia (2.37mg/dL) likely secondary to KD, and she was managed with albumin for 3 days. Lab data on day 7 also showed persistent elevation of inflammatory markers (WBC 15.7 × 1000/uL Neutrophils 44.0% ESR 98 mm/hr CRP 287.13 mg/L, Plt 100 × 1000/uL). Due to persistent fever and poor resolution of inflammatory markers, the patient was given a second dose of IVIG 2g/kg/dose on day 8.

After 11 days of illness, despite 2 doses of IVIG, the patient experienced another temperature of 38.7°C. Lab data was rechecked again on day 11, and showed persistent leukocytosis and elevation of

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inflammatory markers (WBC 28.6 × 1000/uL Neutrophils 54.5% ESR 86mm/hr CRP 65.96 mg/L Plts 299 × 1000/uL). The patient was then started on methylprednisone pulse therapy at 30mg/kg/dose once a day for three days from day 12 to day 15.

A second echocardiogram was performed on 13 days after initial disease onset. Despite the earlier interventions, significant coronary artery dilatation was revealed, with a LCA saccular form aneurysm formation of 5.3mm, and RCA fusiform dilatation of 2.9 mm. Given this risk, cardiology advised dual anti-platelet therapy, and thus clopidogrel was added.

Use of etanercept

The patient remained febrile on day 16, and laboratory values were rechecked again which showed only modest improvement of leukocytosis and inflammatory markers (day 16, WBC 25.4 × 1000/uL Neutrophils 58.0% ESR 55mm/hr CRP 22.17mg/L Plts 773 × 1000/uL). However, with ongoing temperatures and previous interventions ineffective in reducing the patient's fever, a more intensive adjunctive therapy was warranted; thus she was given one dose of etanercept at 0.4mg/kg/dose subcutaneously on day 17, with no immediate side effects noted during hospitalization.

The next day, the patient's fever subsided, with no further relapse. . Laboratory values were evaluated again prior to discharge and showed improving values (day 20, WBC 11.8, Neutrophils 61.4%, ESR none, CRP 17.7 mg/L, Plts 638 x 1000/uL). She was discharged on day 21 of her illness.

A follow-up echocardiogram was done on 4th day of discharge (25 days after disease onset), showed partial resolution of both the LCA and RCA diameters, documented as 4.01mm and 1.85mm, respectively. Furthermore, the patient had remained afebrile since discharge from the hospital.

Discussion

Refractory KD is defined as the recurrence of fever 36 hours after the completion of an IVIG infusion [1]. Although not completely understood, preliminary evidence has attributed IVIG resistance to polymorphisms in the inhibitory fc-γ receptor IIb expressed on the surface of monocytes and macrophages [7]. Risk factors of refractory KD can be seen in laboratory data, namely: low hemoglobin levels (<10.0g/dL), elevated neutrophil count (>74%), high band count and hypoalbuminemia [3,8]. As predicted, our patient exhibited 3 of these risk factors during her admission (hemoglobin 9.3g/dL, band count 40% and albumin 2.37mg/dL).

TNF-α is a pleiotropic inflammatory cytokine that has been strongly implicated in the development of aneurysm formation in patients with KD. Levels of circulating TNF-α in acute KD is higher than in patients without disease, and a strong correlation has been observed between the extent of vasculitis and levels of plasma TNF-α [9,10]. Further, TNF-α level are found to be dramatically increased in patients with refractory KD who later develop CAD [9]. In the initial acute stages of the disease, systemic inflammation develops with the occurrence of mass TNF-α production in peripheral blood. As the disease progresses, TNF-α localizes to the coronary vessels, where it is responsible for the signaling of chemokines and adhesion molecules that result in a local inflammatory process. The inflammation of the coronary vessels in addition to persistent TNF-α production results in elastin degradation and vessel wall breakdown, eventually leading to the coronary artery lesions seen in KD [11].

By blocking TNF-α, vasculitic inflammatory processes do not occur, and the development of coronary artery aneurysms is prevented [11]. Infliximab and etanercept are examples of these TNF-α receptor antagonist. More in-depth research has been done on infliximab compared to etanercept. Infliximab has been shown to be valuable in KD in several studies [12,13]. While, consistently shown to be effective in reducing fever in KD, its safety remains uncertain. In a prospective randomized trial by Burns et al., infliximab was shown to be well tolerated in children below the age of 12 months, and had similar efficacy to the use of a second dose of IVIG when patients were resistant to the first dose of IVIG [12]. However, the randomized controlled ATTACH (Anti-TNF-α Therapy Against Chronic Heart failure) trial which explored the use of infliximab in patients with chronic heart failure was terminated prematurely due to an increase in morbidity and mortality [14]. Etanercept, although a TNF-α antagonist, has different mechanisms to infliximab. Infliximab is a chimeric monoclonal immunoglobulin-G (IgG) antibody that targets transmembrane TNF-α. This damages the cells which express TNF-α, including cardiomyocytes [15]. On the other hand, etanercept is a soluble fusion protein receptor that works more broadly on TNF (both TNF-α and lymphotoxin), and binds to only circulating TNF-α, thereby avoiding the adverse effect seen in infliximab [16]. In the first pilot trial of etanercept in KD by Choueiter et al., etanercept was shown to be safe and well-tolerated in their population sample (6 months – 5 years), with no adverse events noted during the study. In the study, fifteen children with KD received IVIG and high dose aspirin. In addition, etanercept 0.8mg/kg/dose was administered immediately after the first IVIG dose, with 2 further doses given 1 week apart. No recurrent fevers were noted in the subjects, and improvements in coronary artery dilatation were noted in all patients with coronary artery lesions [5]. However, there are currently no studies that can confirm optimal dosing or timing of etanercept therapy in patients with KD. In case report of a 3 month old patient with IVIG resistant KD who also received methylprednisolone pulse therapy, etanercept at 0.8mg/kg/dose weekly was found to be effective when initiated 51 days after initial disease onset leading to reduction of both inflammatory markers and resolution of coronary aneurysms [17]. The patient in our case report received etanercept 0.4mg/kg/dose once, with no recurrent fever or immediate side effects afterwards. Her follow up echocardiogram after the administration of etanercept showed significant improvement (4.01mm compared to 5.3mm prior to etanercept). Although the dose used in our patient (0.4mg/kg/dose) is lower than previously mentioned reports; it is similar to the dosing used in patients with juvenile idiopathic arthritis (0.4mg/kg/dose, biweekly). Our case illustrates that a lower dose of Etanercept (0.4mg/kg/dose) may be equally effective in patients with KD.

Research into the relationship between coronary arteritis and TNF-α was also done in animals models. Wild-type mice were injected with *Lactobacillus casei* cell wall extract, an inducer of coronary arteritis similar in presentation to Kawasaki-type CAD in humans. In mice later injected with etanercept, there was resistance to the development of coronary arteritis, and no inflammation was observed in the cardiac tissue. In contrast, mice given placebos had

large amounts of cellular infiltrates in their cardiac tissue [11]. In another study, blocking TNF-α in murine models not only reduced levels of TNF-α but also other pro-inflammatory cytokines. It was speculated that this effect played a role in attenuating inflammation in KD [10].

It is speculated that future trials will be able to provide extensive information on the efficacy and safety of etanercept in young children. Together with predictors of which cases of KD may fail to respond to IVIG, the new evidence may allow novel ways of reducing incidence of IVIG resistance. This report of the first successful use of etanercept in treating refractory KD in Taiwan may pave the way for more prevalent use of TNF-α antagonist in the country.

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