Chapter 4

A CHILD WITH SEVERE RELAPSING KAWASAKI DISEASE RESCUED BY IL-1 RECEPTOR BLOCKADE AND EXTRACORPOREAL MEMBRANE OXYGENATION

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INTRODUCTION
Kawasaki disease (KD) is an acute inflammatory vasculitis that predominantly occurs in children under 5 years of age\(^1\). The disease is associated with the development of coronary artery aneurysms (CAAs) in 15-25% of untreated cases\(^2\). Standard treatment consists of high-dosed intravenous immunoglobulins (IVIG) along with aspirin\(^3\). About 15% of patients do not respond to a single dose of IVIG and need retreatment\(^4\). When ongoing signs of active disease are present, methylprednisolone pulses are often administered\(^5\). If there is a lack of response to the initial IVIG infusion, alternative anti-inflammatory medication such as infliximab or plasmapheresis have been suggested in individual case series\(^6,7\).

We report, for the first time, on the beneficial use of an interleukin-1 receptor antagonist (IL-1RA) in relapsing KD.

CASE REPORT
A 2-year old boy was presented with persistent fever, coughing and swollen cervical lymph nodes. The boy’s condition had not improved with empirical antibiotic treatment. He developed a rash, conjunctivitis and swollen extremities. Upon admission the child was lethargic boy and he had an increased C reactive protein (340mg/L) (Figure 1). KD was diagnosed, followed by IVIG administration (2g/kg). Tachycardia and hypotension developed the next day. Echocardiography showed diminished shortening fraction of 20% without CAA. Two days later (day 9) he was admitted to the intensive care unit for KD-associated myocarditis and fever. His blood pro-B natriuretic peptide levels had risen to >70 000ng/L (normal value

![Figure 1.](image.png)

**Figure 1.**
Time course of CRP, temperature and treatment in a patient with severe, therapy-resistant Kawasaki disease. IL-1RA was administered in two episodes resulting in a prompt response.

*Abbreviations: CRP=C reactive protein; IL-1RA=interleukin-1 receptor antagonist; IVIG=intravenous immunoglobulin.*
After a second dose of IVIG (2g/kg) he received multiple methylprednisolone pulses with little effect. Echocardiography showed dilatations of the left descending (LAD) and right coronary artery (RCA). At day 14, the patient was intubated because of respiratory and circulatory failure. He had to be supported by extracorporeal membrane oxygenation from day 14 until 17. Fever persisted after decanulation. At day 18, IL-1RA was started (Anakinra once daily; 1mg/kg subcutaneously). The fever disappeared instantly and his coronary status remained stable.

From day 27 onwards, 3 days after the last administration of IL-1RA, the fever recurred. When rash and skin desquamation subsequently reappeared, IVIG with low-dose prednisone was initiated without lasting response. *Escherichia coli* was cultured from his urine. Antibiotics were administered for suspected pyelonephritis and the fever only subsided temporarily. Pulsed methylprednisolone again had no effect. Echocardiography at day 53 showed progression to giant CAAs. At day 54, IL-1RA was restarted and fever again instantly subsided. The maximal coronary artery diameter observed during admission was 6.6mm (z-score 16.9) for the LAD and 7.5mm (z-score 16.2) for the RCA. Representative echocardiography images are shown in Figure 2.

Ten days after IL-1RA was reinitiated the patient was discharged. IL-1RA was continued for 6 weeks, combined with aspirin and coumarin to prevent coronary thrombosis. Coronary angiography after 6 months showed normalization of his coronary arteries (Figure 2), which was unexpected in such a severe case of KD.

**Figure 2.**

Representative echocardiography images of the patient with KD showing a tubular aneurysmatic lesion of the left main coronary artery (diameter 5.5mm: z-score 7.2) and left descending coronary artery (maximal diameter 6.4mm: z-score 16.9) [A] and a saccular aneurysm of the right coronary artery (maximal diameter 6.8 mm: z-score 13.1) [B] during the acute phase. Follow-up conventional coronary angiography at 6 months after discharge showed complete normalization of the coronary artery pathology [C].
DISCUSSION
Several studies have suggested that immune activation and secretion of cytokines contribute to the pathogenesis of KD. Elevated levels of IL-1 have been reported in acute patients and have been correlated to vascular endothelial cell damage\(^6\)\(^{10}\). IVIG treatment has been associated with a decrease in IL-1 levels and it has been shown that IL-1 levels remain elevated in refractory patients\(^9\). These observations suggested a potential role for IL-1R blockers, which is supported by the lasting response to Anakinra observed in our patient. Lee et al recently showed in a mice model for KD that IL-1 is indeed critically involved in coronary arteritis and that CAA development can be prevented by IL-1R blockade\(^11\). This is the first report of the beneficial use of an IL-1RA in patients with KD. Although the clinical recovery may be coincidental, we have observed a clinical response of fever to IL-1RA twice in this patient. Relapse and rapid deterioration of both his clinical and coronary findings after stopping IL-1RA after 7 days suggest its beneficial role in preventing vascular injury from progressing or normalization upon injury.
In summary, this case suggests the potential benefit of IL-1 blockade in patients with refractory KD. Further research regarding the efficacy of IL-1-blockade in KD appears to be warranted.

PATIENT CONSENT
Obtained.
REFERENCES


11. Lee YH, Schulte DJ, Shimada K et al. IL-1beta is Crucial for Induction of Coronary Artery Inflammation in a Mouse Model of Kawasaki Disease. *Circulation* 2012.