**The Use of Infliximab in IVIG-Resistant Kawasaki Disease**

**January 2022**

**Kaitlyn Krebushevski, PGY2**

Kawasaki Disease (KD) is an acute self- limited vasculitis of unknown etiology affecting previously healthy young children usually between the age of 3-5. The diagnosis is made based on a constellation of clinical signs including at least 4 days fever, rash, conjunctival injection, erythema of the lips and oropharynx, edema/ erythema of the hands and feet periungual desquamation- all which are sequalae of systemic inflammation. One of the most feared complications is inflammation of the internal organs including the cardiovascular system. Up to 25% of untreated children go on to develop permanent damage to the coronary arteries due to the infiltration of inflammatory cells into the arterial wall, leading to dilation and aneurysm formation.

The goal of therapy in KD is to reduce this inflammation. Many studies have shown that early treatment with IVIG reduces the incidence of coronary artery aneurysms from 25% to approximately 5%. However, 10–20% of patients will unfortunately be resistant to IVIG, and these patients are at increased risk for developing coronary artery lesions (CALs). IVIG resistance is defined as having a fever at least 36 hours following the end of the initial IVIG infusion. More than any other laboratory value, this fever is universally seen as a marker of persistent inflammation and an indication for additional therapy. Many studies have shown a dose response effect of IVIG and therefore a second dose of IVIG if the most common treatment. The optimal therapy still remains controversial due to the lack of sufficiently powered RCTs. Therapies have included intravenous methylprednisolone, oral corticosteroids, infliximab, cyclophosphamide, cyclosporine and more. TNF inhibitors, such as infliximab have potent anti-inflammatory affects and are used in the treatment of other vasculitis and inflammatory diseases. Additionally, it has been shown that there are elevated levels of TNF alpha in the blood of patients with KD and these levels are correlated with increased risk of CALs. This lead to the question, is there any role for the use of infliximab as initial retreatment in IVIG resistant KD?

A literature search was conducted using a PubMed search with the following MeSH terms “Treatment Resistant Kawasaki Disease” or “Refractory Kawasaki Disease” or “IVIG Resistant Kawasaki Disease” and “Infliximab.” The search was narrowed down to the last 10 years, pediatric population and specifically filtered to look at meta-analysis, systematic reviews, reviews and randomized control trials. Four articles were found that further discussed the use of infliximab for the first retreatment in patients who were refractory to initial treatment with IVIG.

The first study by Mori et al (2018) was a phase 3 randomized open labeled, parallel group multi center trial conducted in Japan. The authors found that patients treated with infliximab as initial retreatment had a lower rate of fever returning after 48 hours (absolute risk reduction of 36% number needed to treat of 2.8). They also looked at coronary arteries z scores on echocardiogram reports through day 56 of illness. There was no significant difference between the dimensions of coronary arteries or aneurysms at the start or end of the study. The limitations to this study included a small sample size. About half of the patients were removed from the study due to the development of worsening KD.

The second study by Son et al (2011) was a retrospective review conducted from two medical centers. They included patients that either received infliximab or IVIG as initial retreatment after IVIG. This study reported that patients treated with infliximab had fewer total days of fever than those treated with infliximab (8 day versus 10 days, p value 0.28) however confidence intervals overlapped between the two groups. Regarding coronary artery z scores, they found no significant difference in the change in dimension from baseline to follow up echocardiogram. The infliximab and IVIG re-treatment groups did not differ significantly in the percentage of patients with aneurysms. The limitations of this study were that it was a retrospective review therefore was not randomized or controlled.

The third study evaluated was a multicenter randomized control trial by Burns et al published in 2021. In this trial, patients (aged 4 weeks to 17 years) with IVIG resistant Kawasaki disease were recruited from 30 hospitals across the USA. Patients were randomly assigned to second IVIG or infliximab. They found that patients in the IVIG group had a higher rate of persistent fever 48 hours to 7 days after initial treatment (ARR of 25% and NNT of 3). With regards to coronary artery dimensions, they found that there was no difference in median coronary artery z scores between the two groups at baseline or at study completion. There was no difference in the number of patients who had a maximal z score of > 2.5 cm or patients whose coronary arteries increased by 0.5% standard deviations. This study was the largest randomized control trial done thus far on this topic.

The last study that was evaluated was an indirect comparison meta-analysis by Chan et al (2019). They found that infliximab was not significantly more beneficial than second IVIG infusion with respect to reducing the total incidence rate of CALs in patients with IVIG resistant KD. With regards to antipyretic effects infliximab was associated with significant antipyretic effects compared to a second IVIG infusion.

[TNF inhibitors](https://www-sciencedirect-com.proxy.library.stonybrook.edu/topics/medicine-and-dentistry/tnf-inhibitor), including infliximab, have potent [anti-inflammatory effects](https://www-sciencedirect-com.proxy.library.stonybrook.edu/topics/medicine-and-dentistry/antiinflammatory-activity). Blockade of the inflammatory cascade at the level of TNF alpha seems to be a logical step in the treatment of KD because elevated levels of this cytokine have been found in the blood of these patients. From these studies that were explored, it seems that infliximab has the potential to have more potent anti pyretic properties, representing decreased inflammation and decreased need for addition retreatment. However, patients’ coronary artery outcomes did not differ in the treatment groups, therefore, making it likely that it is less effective at halting the inflammation at the vessel wall. Larger randomized control trials with longer follow up times need to be performed. Additionally, much of the literature only includes lower risk patients, with higher risk patients removed and treated at provider discretion. Given that infliximab has already been shown to be safe and effective, further investigation is warranted, especially because IVIG is not without harm. A study published in 2020 evaluated the cost between IVIG and infliximab based on expense of medication, dose of medication, infusion time, monitoring time. They concluded that the cost of infliximab is nearly half. Additionally, much of the literature states that IVIG and infliximab have similar safety profiles and adverse effects. Overall, infliximab seems to be a safe, well tolerated and effective alternative treatment option for patients with IVIG resistant Kawasaki Disease.

Burns JC, Roberts SC, Tremoulet AH, He F, Printz BF, Ashouri N, Jain SS, Michalik DE, Sharma K, Truong DT, Wood JB, Kim KK, Jain S; KIDCARE Multicenter Study Group. Infliximab versus second intravenous immunoglobulin for treatment of resistant Kawasaki disease in the USA (KIDCARE): a randomised, multicentre comparative effectiveness trial. Lancet Child Adolesc Health. 2021 Dec;5(12):852-861. doi: 10.1016/S2352-4642(21)00270-4. PMID: 34715057.

Chan H, Chi H, You H, Wang M, Zhang G, Yang H, Li Q. Indirect-comparison meta-analysis of treatment options for patients with refractory Kawasaki disease. BMC Pediatr. 2019 May 17;19(1):158. doi: 10.1186/s12887-019-1504-9. PMID: 31101091; PMCID: PMC6524334.

Johnson SC, Williams DC, Brinton D, Chew M, Simpson A, Andrews AL. A Cost Comparison of Infliximab Versus Intravenous Immunoglobulin for Refractory Kawasaki Disease Treatment. Hosp Pediatr. 2021 Jan;11(1):88-93. doi: 10.1542/hpeds.2020-0188. Epub 2020 Dec 8. PMID: 33293266; PMCID: PMC7769204.

Mori M, Hara T, Kikuchi M, Shimizu H, Miyamoto T, Iwashima S, Oonishi T, Hashimoto K, Kobayashi N, Waki K, Suzuki Y, Otsubo Y, Yamada H, Ishikawa C, Kato T, Fuse S. Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. Sci Rep. 2018 Jan 31;8(1):1994. doi: 10.1038/s41598-017-18387-7. PMID: 29386515; PMCID: PMC5792468.

Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. J Am Coll Cardiol. 2016 Apr 12;67(14):1738-49. doi: 10.1016/j.jacc.2015.12.073. PMID: 27056781.

Son MB, Gauvreau K, Burns JC, Corinaldesi E, Tremoulet AH, Watson VE, Baker A, Fulton DR, Sundel RP, Newburger JW. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. J Pediatr. 2011 Apr;158(4):644-649.e1. doi: 10.1016/j.jpeds.2010.10.012. Epub 2010 Dec 3. PMID: 21129756.