**THE EFFECTIVENESS OF IVIG ON TREATING KAWASAKI DISEASE AND, PREVENTING CARDIAC ANEURYSM: A REVIEW ARTICLE**

Shahad Abdullah AlMansour*, Alaa Sulaiman AOqail, Shomoukh abdulrahman AlNashmi, Rand Abdulrahman AlHaweal and Hayfa Saleh Alabdulkarim

Molida Street, Riyadh.

*Corresponding Author: Shahad Abdullah AlMansour
Molida Street, Riyadh

**ABSTRACT**

Kawasaki disease is one of the common vasculitides in childhood. Many children worldwide are suffering from Kawasaki disease and many lines of treatment are currently given. In this review, we discussed IVIG, either with aspirin or corticosteroids, or even only corticosteroids. Since the quantity of the dose is very important, studies show that an initial high quantity is more efficacious than a low initial quantity by avoiding the non-response consequences, which can potentially lead to the formation of coronary artery lesion (CAL) and coronary aneurysms. Furthermore, the treatment is also time sensitive, which means that is important to be taken as early as possible and not after the beginning of the non-responsive state, and specifically until the 7th day of continuous fever. Other studies have also demonstrated that except of the time and quantity, the existence of not of certain polymorphisms can play an important role in the expression of the non-responsive state. In cases were the individual patient has reached his/her non-responsive state, it has been shown that IVIG is still effective and can decrease the formation of CAL and thus coronary artery aneurysms. So, in order to perform and achieve the better possible result, it is very important to take all the aforementioned steps into account.

**KEYWORDS:** Kawasaki disease, vasculitides.

**INTRODUCTION**

**General characteristics and epidemiology.**

The Kawasaki disease is common among children between the ages of 6 months and 5 years. According to Nakamura et al 2012, and Gorczyca et al 2014, most of the affected children usually come from the industrialized countries. The disease is as a result of the acute vasculitis of the small and medium arteries, and according to Gorczyca, the causes of this condition have not yet been determined. The Kawasaki disease may lead to coronary artery lesion (CAL), in cases where the initial treatment doesn’t work. According to Ogino et al. (2012), CAL may have fatal consequences for the children. Development of coronal aneurysm is observed in the cute phase of the Kawasaki disease. Coronal aneurysm is the most common type of CAL (Rowley & Shulman 2010).

Although cases of the Kawasaki disease have been documented across all ethnic groups, children from Asia are the most affected (Onuchi 2009). Among the vulnerable Asian children, those mostly affected have been found to be living a western lifestyle. This brings the aspect of genetics up for considerations. According to a study conducted in Japan, incidents of the Kawasaki disease have been increasing in a linear mode until the year 2010 (Nakamura et al. 2012). Apoptotic and inflammatory genes have been identified as the main causes of the high vulnerability levels.

**Pathogenesis**

Studies carried out show that the disease mainly affects tissues and organs such as, the respiratory organs, gastrointestinal, cardiovascular, and the nervous system (Amano et al. 1980). The disease was initially associated with endothelial cell antigens. However, more studies have led to the belief that an infectious agent can infect many individuals, leaving no symptoms behind. According to Rowley et al. (2008), the availability of a genetic background may allow the infection to progress to the Kawasaki disease.

Contrary to the initial expectations of the neutrophils, the macrophages, mononuclear, and lymphocytes, are the predominant cell types at the cellular level (Rowley et al. 2000). The study also revealed that arterial walls contain IgM and IgG plasma cells, despite the fact that the IgA plasma cells are significantly higher in numbers. The findings revealed that the agent causing Kawasaki diseases goes through the respiratory tract, and provokes an IgA immune response that eventually spreads to the vascular tissue.
Diagnosis
The American Heart Association in 2004 defined the guidelines for the diagnosis, and treatment of Kawasaki disease at the acute phase. The guidelines also highlighted on how to handle Kawasaki disease patients in the long-term. According to the guidelines, the symptoms include a five-day long fever, and not less than four of the principal clinic characteristics. For example, a patient may have changes in the lips, polymorphous skin rash, and distal extremities alterations. In some cases, a patient may experience a fever for a long time without the other symptoms. This is referred to as an incomplete Kawasaki disease diagnosis. According to Jane W. Newburger et al. (2004), the incomplete diagnosis is caused by an abnormal coronary artery, as indicated by endoangiography findings.

Therapeutic Strategies
 Intravenous immunoglobulin IVIG has been found to be the most common therapeutic strategy. In the early stages of the infection, it is administered in a 5-10 days range (Galeotti et al. 2010). Alongside lowering or eliminating the fever, the therapeutic strategy lowers the rate of provocation of the coronary artery aneurysms. For the treatment to work effectively, it is advisable for the patient to take it within the first 7-10 days.

Aspirin is also used for treatment as it contains anti-thrombotic and anti-inflammatory properties. It is usually merged with IVIG administration and administered during the acute phase. According to Baumer et al. (2006), the administration of aspirin boosts the anti-inflammatory properties of IVIG. In cases of patients with abnormalities in the coronary artery, aspirin or anti-platelet are included in the treatment depending on the severity of the abnormalities. According to Jane W. Newburger et al. (2004), this helps to avoid thromboses which may result from the abnormal blood flow.

Corticosteroids are also used as a therapeutic strategy due to their important capabilities of reducing fever. Use of corticosteroids was initially proposed in case the IVIG treatment failed. Discussed in detail below is a better therapeutic strategy, which entails a steroid pulse with the initial administration of IVIG (Galeotti et al. 2010).

IVIG – Mechanism of Action
IVIG is an immunoglobulin IgG consisting of various specificities. The production process entails the purification of plasma donated by many healthy donors. According to Galeotti et al. (2010), immunoglobulins were initially intended for immunodeficiency treatment, but they also work well in this case, with no side effects. Furusho et al. (1984), was the first to write a report that identified IVIG as suitable treatment for Kawasaki disease. When it comes to the mechanism of action, IVIG has several aspects. For instance, since endothelial cells are instrumental in the pathology of Kawasaki disease, IVIG can inhibit and modulate their functions (Huyen et al. 2001). IVIG also inhibits the adhesion of B-lymphocyte to fibronectin According to Vassilev et al. (1999) this results in IgG antibodies, which facilitates the anti-inflammatory effects of IVIG in Kawasaki disease. These mechanisms play an important role as they reduce the activation of the immune, and also the possibility of coronary artery abnormalities.

Effectiveness of IVIG
IVIG is usually included in the first line of treatment because of its capabilities of reducing coronal artery aneurysm incidences as they can be fatal to the child. Coronal artery aneurysm is mostly common among patients who don’t respond to the initial IVIG treatment. Studies carried out show that a slight difference or additional of the IVIG dose can help avoid the formation of coronary artery aneurysm. Newburger et al. (2004), carried out a randomized trial consisting of 549 children with the Kawasaki disease at its acute phase. The study revealed that a large IVIG dose was enough and effective in reducing the occurrence of coronal artery aneurysms.

Durongpisitkul et al. (1995) also carried out a study and made observations on the effects of aspirin and IVIG on coronal artery aneurysms. The study entailed two groups, one which received IVIG, and another one that did not receive. According to the results, the group that received IVIG had lower rates of coronal artery aneurysms than the group that did not receive. The study however did not show any statistical significance of the IVIG doses and the decrease in aneurysm formation.

There are other studies that have investigated and revealed the relation between the aneurysm episodes and the administered IVIG dose. Most of the studies carried out state that a dose of 1g/kg is sufficient for Kawasaki disease treatment and the avoidance of aneurysm formation (Gorczyca et al. 2014; Lin et al 2013). According to Jane W. Newburger et al. (2004), the infusion of a 2g/kg IVIG dose instead of a 1g/kg resulted in a more rapid decrease of the symptoms. A higher dose proved to be more effective in the treatment of Kawasaki and prevention of coronary artery aneurysms. Due to this, the current standard protocol for the treatment of Kawasaki disease is a single 2g/kg IVIG dose.

Most of the children affected by Kawasaki disease usually overcome it with the initial IVIG treatment. However, 10% of the infected children tend to have persistent fever and do not respond to IVIG treatment. These are cases with coronary artery lesions (CAL) formation (Wang et al. 2013). Treatment for such cases can be continued with IVIG administration or changed to other forms of treatment such as corticosteroids. According to Adachi et al. (2010), a study revealed that the combination of corticosteroids and IVIG dosage has a positive effect on patients with coronary artery aneurysms that did not respond to the initial IVIG therapy. The study revealed that although IVIG can be used to avoid the formation of aneurysms, adding corticosteroids enhances the function.
Hashino et al. (2001) carried out a study that entailed Kawasaki patients who did not respond to the initial IVIG treatment. The patients were divided into two groups; one which was treated with additional IVIG, and a second group which was treated with steroid pulse therapy. In the results of the study, 63% of patients in the first group developed coronary artery lesions (CAL). In the second group, 78% of the patients were found to have also developed CAL. The researchers concluded that the administration of steroids results in a higher possibility of CAL formation. This is because steroids restrain cytokines production, which according to Hashino et al. (2010), enable the regeneration of the inflamed coronary artery wall.

Wei et al. (2015) carried out a study aimed at investigating IVIG dosage and CAL formation among patients who don’t respond to the initial treatment. According to Fukunish et al. (2000), patients may fail to respond to the initial IVIG treatment if it is administered in low doses, or if the dose is not administered properly. The researchers in this case aimed at avoiding this and started by administering high doses. For patients who do not receive the treatment appropriately, it was determined that it would be risky for them to receive the next set of treatment as the risk of getting CAL would be high. Thus, the research team decided to combine the initial IVIG treatment with immunosuppressive agents, especially for the patients that were at a higher risk. According to Abe et al. (2008), the polycythemia rubra vera I granulocyte colony-stimulating factor can be used to identify whether the patient might be responsive to treatment or not. This strategy increases the chances of a patient accepting the treatment and avoiding CAL formation.

Many studies have been carried out and the main area of concern remains to be the formation of CAL. This has raised questions on how CAL is formed and the possible strategies to overcome it. Ogino et al (2012), carried out a study based on treating Kawasaki patients with CAL formation, by using steroids or IVIG. Results of the study showed that the use of IVIG resulted in a better chance in overcoming CAL formation.

Lin et al. (2013) also conducted a study aimed at investigating the effects of IVIG on CAL formation. According to the study, beta-propiolactonation posed a huge risk to IVIG response among the patients. The study also revealed that the acidification was beneficial to the IVIG treatment as it reduced the risk of non-response. The only problem with this according to the study is that acidification tends to increase coronary aneurysms. This is caused by the damage of elastin, which weakens the blood vessels (Lin et al. 2013).

Onouchy et al. (2013), carried out a study that revealed the effectiveness of IVIG treatment to not be affected by dosage or time of administration. According to Onouchy et al., the formation of CAL and unresponsiveness to treatment is as a result of two polymorphisms namely ITPKC and CAPS3. Results of the study showed that patients who had the two SNPs alleles in excess did not respond to both the initial and additional IVIG treatment. The results of this study added another facet for consideration in the pathology of Kawasaki disease.

Kaneko et al. (2011) study focused on a biomarker that can differentiate CAL formation. Several studies have tried to achieve the development of the tool but all have failed. The study by Kaneko et al only insinuated the theoretical framework of the tool.

CONCLUSION

The Kawasaki disease affects many children from different parts of the world. Currently, there are several lines of treatment available for combating the disease. IVIG has been identified as an effective treatment, alongside corticosteroids or aspirins. Corticosteroids alone have also been found to be effective in treatment. Non-response to treatment can be avoided by ensuring the right dosage quantity is administered. Non-response to treatment leads to CAL and coronary aneurysms, which may be fatal to the patients. Treatment of the Kawasaki disease should commence as early as possible. Once the patient reaches the non-responsive state, or the fever lasts for more than 7 days, initial treatment should be halted. At the non-responsive stage, IVIG treatment has been found to be still effective in reducing CAL formations and coronary artery aneurysms. It is important to take all the steps mentioned above in treatment, so as to achieve the best possible results.

REFERENCES


