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RESEARCH LETTER

Use of Infliximab in Infantile Kawasaki Disease: Experiences over 8 Years

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Abstract

Data on the use of infliximab (IFX) in infants with Kawasaki disease (KD) are scant. We retrospectively analyzed data of 35 infants with KD who received IFX. Effectiveness of IFX was assessed in the presence of intravenous immunoglobulin (IVIG) resistance and coronary artery aneurysm (CAA) regression. Fifteen of thirty-five received IFX in the presence of IVIG resistance; nineteen of thirty-five for CAA; and one for persistently high c-reactive protein. Thirteen out of fifteen with IVIG resistance became afebrile by 24 h. Twelve medium CAA regressed over 3 months, four of ten giant CAA normalized, and three regressed to small CAA, median time being 7.5 (3.5, 18) months. IFX was well-tolerated, safe, and effective in infants with KD.

Keywords Anti-tumor necrosis factor-alpha · Coronary artery aneurysm · IVIG resistance · Refractory Kawasaki disease · TNF-α

Kawasaki disease (KD) is an acute medium vessel vasculitis predominantly in under-five children. Infants usually present with incomplete KD leading to a delay in diagnosis and initiation of treatment, thereby increasing the risk of developing coronary artery aneurysms (CAAs). 10–20% of KD do not respond to high-dose bolus intravenous immunoglobulin (IVIG) which remains the gold standard of treatment. Infliximab (IFX), a tumor necrosis factor blocker, is recommended for treating IVIG resistance as well as for treatment intensification in patients presenting with aneurysms at diagnosis [1–4]. Although infants with KD constitute the most vulnerable group, with a high incidence of IVIG resistance as well as CAAs, there is paucity of literature on the use of IFX in infancy.

This is a retrospective observational study which included infants diagnosed with KD and treated with IFX between January 2016 and December 2024. Indications for IFX included IVIG resistance (persistent or recrudescent fever ≥ 36 h after completion of initial IVIG infusion), or presence of CAAs at diagnosis, or an increase in size of CAA following IVIG therapy [5]. Response to IFX was assessed in terms of fever defervescence and normalization of inflammatory markers, regression or reduction in size of CAAs. Any side effects of IFX were also noted. Between 2016 and 2019, IFX was administered as 5 mg/kg single intravenous infusion; however, since 2020, the dose of IFX was increased to 10 mg/kg single intravenous infusion [6]. Data were collected from hospital records. Clinical characteristics and echocardiographic follow-up outcomes were analyzed.

During the study period, 292 children (61 infants) were diagnosed with KD and 35 of these infants (29 boys, 6 girls) received IFX. Data of infants who received IFX were analyzed. Table 1 depicts the clinical profile of these 35 infants (median age 6 months). Overall, 15 were < 6-month-old and the youngest IFX recipient was 6-week-old who presented with shock. This infant was initially diagnosed as septic shock and on day 12, the diagnosis was revised because of persistent fever, elevated c-reactive protein (CRP) with progressive thrombocytosis. IFX was administered on day 14 because of giant aneurysms.

The mean (SD) duration of illness at presentation was 7.4 (4.5) days. The mean (SD) time for administration of IFX was 14.6 (6.5) days from the onset of fever. Fifteen infants received for IVIG resistance. A 2-month-old infant, though afebrile, received IFX in view of serial increase in

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Table 1 Characteristics of infantile KD treated with infliximab ($n=35$)

Characteristic	Value
Male gender[a]	29 (82.8)
Indications for IFX[a]	
IVIG resistance	12 (34.3)
CAA at presentation	17 (48.6)
IVIG resistance + CAA	3 (8.6)
Persistently high CRP post-IVIG	1 (2.8)
Increase in CAA diameter post-IVIG	2 (5.7)
Duration of fever[b]	
Prior to IVIG (days)	7.4 (4.5)
Prior to IFX (days)	14.6 (6.5)
Response to IFX[a]	
Defervescence of fever	15/15 (100)
Decrease in CRP	34/35 (97)
Decrease in CAAs[a],[c]	19/22 (86)
Median duration of CAA resolution in infants < 6 months (months)[d]	6 (2.5, 13.5)
Median duration of CAA resolution in infants ≥ 6 months (months)[d]	8 (3, 15)

CAA coronary artery aneurysm, *IFX* infliximab, *IVIG* intravenous immunoglobulin

Values expressed as [a]*n* (%), [b]mean (SD) [d]median(Q1, Q3)

[c]Complete regression 16, partial regression 3, loss to follow-up 2, persistent CAA 1

CRP post-IVIG. Following IFX administration in IVIG-resistant infants, fever subsided within 24 h in 13 patients and the remaining 2 were afebrile after 48 h. CRP normalized within 48 h of administration in all except one infant who took about 72 h.

Out of 19 infants who received IFX for CAA, 17 had CAA at presentation and 2 who had a normal echocardiogram at presentation, developed CAA post-IVIG. Sixteen infants had > 1 CAA. Overall, 12 CAAs were medium-sized and 10 were giant CAAs. CAAs were most commonly seen in LMCA (left main coronary artery), followed by involvement of LAD (left anterior descending artery) and RCA (right coronary artery). Medium and giant CAAs were most commonly seen in LAD followed by LMCA and RCA. All the medium-sized CAAs completely regressed over a median follow-up of 3 months. Four giant aneurysms completely regressed, and three reduced to small aneurysms; the median time for giant CAAs to regress was 7.5 months (Q1 is 3.5, Q3 is 18). One 2-month-old infant diagnosed after 20 days was IVIG-resistant and received IFX on day 22 and continued to have a persistent giant aneurysm. Two infants with giant aneurysms were lost to follow-up. There were no adverse reactions to IFX. None of the infants had any incidence of infection on follow-up.

Infliximab is a well-accepted modality for treating IVIG-resistant KD [1, 7, 8]. Likewise, in children with CAA at diagnosis, treatment intensification with IFX or steroids have been proposed [2–4, 8]. In a two-center retrospective study of IVIG-resistant disease, re-treatment with IFX resulted in faster fever resolution and fewer days of hospitalization than did a second IVIG [1]. In a double blinded, placebo controlled randomized trial, addition of IFX to primary treatment did not reduce IVIG resistance, but resulted in a reduction in the number of days of fever, markers of inflammation, LAD coronary artery Z-scores, and IVIG reaction rates [9].

Dionne, et al. retrospectively analyzed addition of IFX or corticosteroids to IVIG in patients who had CAA *Z*-score ≥ 2.5 to < 10 at the time of diagnosis [2]. They noted that intensification with either IFX or corticosteroids resulted in lesser progression of CAA in comparison to IVIG alone with similar rates of CAA regression in both groups. However, 102 of total 121 patients recruited had only small aneurysms and none had giant CAA.

In this study, addition of IFX in IVIG-resistant infants resulted in cessation of fever and normalization of CRP within 48 h. CAAs at diagnosis treated with IFX resulted in no further increase in size. On echocardiographic follow-up, there was regression of all medium and even four giant CAAs to normal size; three giant CAAs regressed to small aneurysms. It is important to note that during follow-up, none of these infants developed tuberculosis or any other significant infection [10].

The limitations of this study include the retrospective observational nature of data from a single center with a small study population. The study, however, reinforces that IFX can be considered a safe and effective treatment in infantile KD.

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Author Contributions PP conceptualized and initiated the study. RPG, RS, AN, and JB collected the data, and all authors participated in drafting the manuscript.

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Data Availability Additional information may be requested from the corresponding author.

Conflict of interest None.

Ethics Approval Institutional Ethics Committee, Institute of Child Health; Ref No: IEC/222/2020, dated Jan 20, 2021.

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