Background and Objectives: We investigated the status of infliximab use in intravenous immunoglobulin (IVIG)-resistant Kawasaki disease (KD) patients and the incidence of coronary artery aneurysms (CAAs) according to treatment regimens.

Methods: Between March 2010 and February 2017, 16 hospitals participated in this study. A total of 102 (32.3±19.9 months, 72 males) who received infliximab at any time after first IVIG treatment failure were enrolled. Data were retrospectively collected using a questionnaire.

Results: Subjects were divided into two groups according to the timing of infliximab administration. Early treatment (group 1) had shorter fever duration (10.5±4.4 days) until infliximab infusion than that in late treatment (group 2) (16.4±4.5 days; p<0.001). We investigated the response rate to infliximab and the incidence of significant CAA (z-score >5). Overall response rate to infliximab was 89/102 (87.3%) and the incidence of significant CAA was lower in group 1 than in group 2 (1/42 [2.4%] vs. 17/60 [28.3%], p<0.001).

Conclusions: This study suggests that the early administration of infliximab may reduce the incidence of significant CAA in patients with IVIG-resistant KD. However, further prospective randomized studies with larger sample sizes are required.

Keywords: Kawasaki disease; Coronary artery; Infliximab; Intravenous immunoglobulins

INTRODUCTION

Approximately 10–20% of patients with Kawasaki disease (KD) are resistant to treatment with initial intravenous immunoglobulin (IVIG). IVIG is the accepted first-line therapy for children with KD; however, there is no consensus on the treatment of patients with IVIG-resistant KD suffering from persistent fever despite the initial dose of IVIG. Patients who are resistant to initial IVIG are at an increased risk of developing coronary artery aneurysms (CAAs). Infliximab has been used late in most patients with IVIG-refractory KD, and it
appears that early addition of infliximab as a safe and well-tolerated treatment reduced fever duration, several inflammation markers, and the left anterior descending coronary artery (CA) z-score. We performed a study to examine the efficacy of infliximab treatment in IVIG-resistant KD patients during the past eight years in Korea and investigate the incidence of CA complications in relation to treatment regimens.

METHODS

We performed a retrospective study on 102 patients diagnosed with IVIG-resistant KD between March 2010 and February 2017 at 16 hospitals. We performed a survey by sending a questionnaire to the institutions where infliximab was used at any time after the first IVIG treatment failure in patients with KD to obtain data on patient background, medical treatments, and outcomes. All hospitalized patients were initially treated with IVIG (2 g/kg). All patients received aspirin at a dose of 30 to 100 mg/kg/day until they were afebrile for at least 48 to 72 hours, at which point the aspirin dose was reduced to 3 to 5 mg/kg/day. We defined initial IVIG-resistant treatment failure as persistent or recrudescent fever at least 36 hours after completion of the first IVIG infusion. Response to infliximab treatment was defined as cessation of fever within 48 hours of infliximab infusion. In the present study, the dose of infliximab was 5 mg/kg, IVIG 2 g/kg, intravenous methylprednisolone pulse (IVMP) 30 mg/kg/dose, oral prednisolone 1 g/kg, and methotrexate (MTX) 10 mg/body surface area. Demographic data included patient sex, date of birth, date of KD diagnosis, and the date of infliximab treatment. KD was diagnosed according to the criteria published by the American Heart Association. The CA complications were assessed using echocardiography. We compared Z-max scores (maximum internal diameter of the right and left or left anterior descending CA expressed as standard deviation units from the mean [z-score] normalized for body surface area) obtained within 12 weeks after onset from each center. The calculation of z-scores for CA measurements was accomplished using the z-score calculator. We investigated the response rate to infliximab and the incidence of significant CAA (larger than medium, z-score >5). Subjects were divided into two groups according to the period from onset of fever to infliximab administration: early treatment (group 1) and late treatment (group 2). Group 1 included patients treated with infliximab after first IVIG treatment and after second IVIG treatment. Group 2 included patients treated with infliximab after second IVIG treatment followed by IVMP, after first IVIG treatment followed by IVIG plus IVMP, and after first IVIG followed by IVMP. We compared the clinical characteristics, laboratory findings, and echocardiographic findings according to the specific treatment regimens in each group. We excluded one case treated with infliximab after first IVIG treatment because IVIG treatment was provided at a dose of 400 mg/kg for 5 days. This study was approved by the Ethics Committee of the Inje University, Haeundae Paik Hospital (HPIRB201801011001).

Statistical analyses

Statistical analysis was performed using the SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). The χ² test was used to compare the categorical data by gender, incomplete KD ratio, infliximab response rate, and CAA z-score >5. Quantitative data with a normal distribution are presented as mean±standard deviation. To compare the continuous data of 2 types of treatment regimens, the Student’s t-test was performed. To compare 5 types of treatment regimens, the analysis of variance (ANOVA) was used. According to the results of the study, we calculated the odds ratio for the probability of CAA exceeding the z-score of 5 according to the presence or absence of IVMP treatment using logistic regression analysis and normalized
it relative to age and fever duration. A logistic regression analysis was performed on the incidence of significant CAA.

RESULTS

A total of 102 patients (32.29±19.94 months, 72 males) who received infliximab after first IVIG treatment were included (Tables 1 and 2). Fever duration until infliximab infusion in group 1 was shorter than that in group 2 (10.5±4.4 days vs. 16.4±4.5 days, p<0.001) as shown in Table 1.

Table 1. Characteristics of IVIG resistant KD patients in the infliximab group 1 and the group 2

|                | Group 1   | Group 2   | p value |
|----------------|-----------|-----------|---------|
| Sex            |           |           |         |
| Male (%)       | 29 (69.0) | 43 (71.7) | 0.775   |
| Female (%)     | 13 (30.1) | 17 (28.3) |         |
| Age (mon)      | 39.52±21.88 | 28.22±16.17 | 0.007   |
| PMN (%)        | 74.90±19.55 | 72.51±15.52 | 0.794   |
| Albumin (g/dL) | 3.56±0.47 | 3.51±0.56 | 0.939   |
| Total bilirubin (g/dL) | 1.54±1.31 | 1.67±1.50 | 0.672   |
| AST (IU/L)     | 148.18±130.97 | 168.43±258.90 | 0.857   |
| ALT (IU/L)     | 174.00±181.84 | 173.76±161.56 | 0.629   |
| CRP (mg/dL)    | 11.75±7.38 | 12.29±7.26 | 0.654   |
| NT-proBNP (pg/dL) | 1,598.81±1,672.20 | 1,696.58±1,590.02 | 0.791   |
| Incomplete KD  | 12 (28.6) | 10 (16.7) | 0.150   |
| Fever duration until 1st IVIG (day) | 4.69±1.65 | 4.93±1.45 | 0.327   |
| Fever duration until infliximab infusion (day) | 10.52±4.39 | 16.43±4.53 | <0.001  |
| Response to infliximab (%) | 34/42 (80.95) | 55/60 (91.67) | 0.137   |
| CAA, z-score>5 (%) | 1 (2.4) | 15 (25) | 0.002   |

Laboratory results were the results of at the time of diagnosis. Group 1: the patients that received infliximab after first IVIG or second IVIG therapy; Group 2: the patients that received methyl prednisolone pulse therapy after first IVIG or second IVIG therapy.

Table 2. Characteristics of the subgroups of IVIG resistant KD patients treated with infliximab

| Group 1 | IVIG → IVIG → infliximab | IVIG → infliximab | Group 2 | IVIG → IVIG → IVMP → infliximab | IVIG → IVIG + IVMP → infliximab | IVIG → IVMP → infliximab |
|---------|--------------------------|-------------------|---------|---------------------------------|---------------------------------|---------------------------|
| Sex     | Male (%)                 | 29 (69.0)         | 19 (70.4) | 10 (66.7) | 23 (85.1) | 10 (100) |
|         | Female (%)               | 13 (30.1)         | 8 (29.6)  | 5 (33.3)  | 6 (22.2)  | 2 (20)  |
| Age (mon) | 39.52±21.88 | 41.19±25.40 | 36.53±12.87 | 40.00±17.46 | 11.60±7.65 | 10.00±1.00 |
| PMN (%) | 74.90±19.55 | 71.41±22.31 | 80.71±11.66 | 71.51±15.52 | 71.03±15.63 | 71.85±17.15 |
| Albumin (g/dL) | 3.56±0.47 | 3.54±0.54 | 3.39±0.30 | 3.51±0.56 | 3.52±0.59 | 3.61±0.45 |
| Total bilirubin (g/dL) | 1.54±1.31 | 1.61±1.27 | 1.41±1.36 | 1.67±1.50 | 1.66±1.45 | 2.14±1.75 |
| AST (IU/L) | 148.18±130.97 | 162.00±147.46 | 125.33±93.03 | 140.00±248.97 | 285.00±281.00 | 229.50±205.50 |
| ALT (IU/L) | 174.00±181.84 | 185.24±181.93 | 155.27±180.44 | 173.76±161.56 | 285.00±281.00 | 229.50±205.50 |
| CRP (mg/dL) | 11.75±7.38 | 10.09±7.65 | 14.50±5.97 | 12.29±7.26 | 11.79±6.76 | 14.90±8.07 |
| NT-proBNP (pg/dL) | 1,598.81±1,672.20 | 1,834.82±1,672.04 | 1,211.07±1,598.51 | 1,696.58±1,590.02 | 1,808.00±1,753.89 | 550.85±30.65 |
| Incomplete KD (%) | 12 (28.6) | 6 (22.2) | 6 (16.7) | 8 (27) | 1 (9) | 1 (50) |
| Fever duration until 1st IVIG (day) | 4.69±1.65 | 4.89±1.95 | 4.33±0.79 | 4.93±1.45 | 4.89±1.59 | 5.27±0.45 |
| Fever duration until infliximab infusion (day) | 10.52±4.39 | 11.60±4.41 | 7.43±2.13 | 16.43±4.53 | 15.85±2.88 | 18.00±8.17 |
| Response to infliximab (%) | 34/42 (80.95) | 23/27 (85.1) | 11/15 (73.3) | 55/60 (91.67) | 43/47 (91.5) | 10/11 (90.9) |
| CAA, z-score>5 (%) | 1 (2.4) | 1 (3.7) | 0 (0) | 15 (25) | 11/17 (64.7) | 5/11 (50) |

Laboratory data are those at the time of diagnosis. Group 1: patients who received infliximab after first IVIG or second IVIG therapy; Group 2: patients who received methyl prednisolone pulse therapy after first IVIG or second IVIG therapy. Values are presented as number (%) or mean±standard deviation (range). ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAA = coronary artery aneurysm; CRP = C-reactive protein; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; NT-proBNP = N-terminal-pro-brain natriuretic protein; PMN = polymorphonuclear neutrophil.
Group 1 included patients treated with infliximab after first IVIG treatment and after second IVIG treatment. Among 27 patients treated with infliximab after second IVIG treatment, 23 (85.2%) responded to treatment, CAA occurred in one patient (3.7%). Among 15 patients treated with infliximab after first IVIG treatment, 11 (73.3%) responded and no case of CAA was observed. Group 2 included patients treated with infliximab after second IVIG treatment followed by IVMP, after first IVIG treatment followed by IVIG plus IVMP and after first IVIG followed by IVMP. Among 47 patients treated with infliximab after second IVIG treatment followed by IVMP, 43 (91.5%) responded, and 11 (23.4%) patients developed CAA. Among 11 patients treated with infliximab after first IVIG treatment followed by IVIG plus IVMP, 10 (90.9%) responded, and 4 (36.4%) developed CAA. One patient who did not respond to oral MTX after IVIG plus IVMP treatment responded to infliximab. But another patient who did not respond to infliximab after IVIG plus IVMP treatment responded to oral MTX. Among 2 patients treated with infliximab after first IVIG followed by IVMP, 2 (100%) responded, and 1 (50%) developed CAA. Overall response rate to infliximab was 89/102 (87.3%). CAA incidence was significantly lower in group 1 than in group 2 (1/42 [2.4%] vs. 17/60 [28.3%], p<0.001) (Table 3, Figure 1).

Multivariate logistic regression analysis (Table 4) showed that late infliximab treatment (group 2) was an independent risk factor for CAA (odds ratio [OR], 4.143; 95% confidence interval [CI], 1.284–13.371) whereas early infliximab treatment (group 1) was not. We used ANOVA analysis for continuous data analysis. There was no statistically significant difference between 5 treatment regimens (Table 2). However, multivariate logistic regression analysis (Table 4) showed that the fever duration until infliximab infusion (OR, 2.381; 95% CI, 0.987–5.743) was not an independent risk factor for CAA.

**DISCUSSION**

In the present study, we defined KD patients with significant CAA when its size was more than medium (z-score >5) that can result in major adverse cardiac events and requires long-term medication. Friedman et al.⁸ described the natural history of CAA in US KD patients and identified factors associated with major adverse cardiac events and CAA regression; they found that CAA size at diagnosis is highly predictive of CAA regression rate, with a low CAA

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**Table 3. Responsiveness and the incidence of significant CAA after different infliximab treatment regimens**

| Group | Treatment | Percentage of cases | Responsiveness to infliximab treatment | CAA, z-score >5 |
|-------|-----------|---------------------|----------------------------------------|---------------|
| 1     | IVIG → IVIG → infliximab | 27/102 (26.5%) | 23/27 (85.1%) | 1/27 (3.7%) |
|       | IVIG → infliximab | 15/102 (14.7%) | 11/15 (73.3%) | 0/15 (0%) |
| 2     | IVIG → IVIG → IVMP → infliximab | 47/102 (46%) | 43/47 (91.5%) | 11/47 (23.4%) |
|       | IVIG → IVIG + IVMP → infliximab | 11/102 (10.8%) | 10/11 (90.9%) | 4/11 (36.4%) |
|       | IVIG → IVMP → infliximab | 2/102 (2%) | 2/2 (100%) | 1/2 (50%) |

CAA = coronary artery aneurysm; IVIG = intravenous immunoglobulin; IVMP = intravenous methyl prednisolone.

**Table 4. Logistic regression analysis of the incidence of significant CAA (z-score >5)**

|                         | OR (95% CI) |
|-------------------------|-------------|
| Late infliximab treatment after IVMP |             |
| Not used                | 1 (reference) |
| Used                    | 9.269 (1.041–82.508) |
| Age (months)            | 0.993 (0.959–1.027) |
| Fever duration until infliximab infusion (days) | 1.057 (0.941–1.188) |

CAA = coronary artery aneurysm; CI = confidence interval; IVMP = intravenous methyl prednisolone; OR = odds ratio.
Figure 1. Treatment modalities and response rates to infliximab and incidence of a significant CAA (z-score >5).

CAA = coronary artery aneurysm; IVIG = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; MTX = methotrexate.
regression rate (16%) in patients with large/giant CAA (z-score ≥10) and a high regression rate in those with small CAA (z-score <5.0) at diagnosis (85%).

Many experts recommend retreatment with a second dose of IVIG for IVIG-resistant KD.\textsuperscript{1)} Patients who fail to respond to 2 doses of IVIG present a unique challenge because there is no clear guidance for an appropriate treatment regimen in this small group of refractory KD patients who remain febrile. An alternative approach is either a third dose of IVIG, combined IVMP, or infliximab.

The use of corticosteroids in KD remains controversial. Corticosteroids for KD have been avoided since a retrospective study reported by Kato in 1979 in the pre-IVIG era.\textsuperscript{9)} Others have reported the use of both IVMP and oral corticosteroids with good results, predominantly in patients with refractory KD.\textsuperscript{10)} A recent study on the use of corticosteroids in KD has shown that the use of steroids in the acute phase of KD can be associated with improved CA abnormalities with moderate-quality evidence.\textsuperscript{11)}

However, treating refractory KD with IVMP should be undertaken with caution because of adverse effects.\textsuperscript{12)} Steroid treatment has also been associated with the development of CAA or rupture in many case reports.\textsuperscript{13-16)} A recent study shows that IVIG-resistant patients with alternative corticosteroid therapy more frequently develop coronary artery lesion (CAL) than those without corticosteroid therapy.\textsuperscript{17)} But in our study, physicians might have been more likely to administer pulse steroids rather than infliximab to sicker patients with increased inflammatory markers, because infliximab is not covered by the Korean national health insurance service and more expensive than steroids. Moreover, there has been a reluctance in using infliximab because of a potentially increased malignancy risk. However, it has been reported recently that infliximab exposure is not associated with an increased risk of malignancy in pediatric patients with inflammatory bowel disease.\textsuperscript{18)}

In refractory KD patients, anti-tumor necrosis factor (TNF-\(\alpha\)) agents, such as infliximab, have been investigated. Overall, it appears that infliximab causes rapid defervescence resulting in a shorter length of hospital stay, and is relatively well tolerated. Retrospective studies have reported response rates (defined by a reduction in fever and CRP level) of 81.3–91.7\% when infliximab was used as a second-line agent.\textsuperscript{4-6,19)} In our study, the overall response rate to infliximab treatment was 89/102 (87.3\%).

In our study, among 15 patients with refractory KD who received infliximab after first IVIG treatment, 11 cases were duplicated with prior published data.\textsuperscript{20)} Between 2010 and 2015, 43 patients with refractory KD received either infliximab treatment (n=11) or IVIG retreatment (n=32). In the 11 patients randomized to infliximab, 10 patients (90.9\%) responded. The infliximab group had a shorter duration of fever and fewer days of hospitalization. CA outcomes were similar. In our study, the response rate to infliximab treatment after first IVIG appears to be low (73.3\%), but in previous studies, the reported response rate to infliximab was 81.3–91.7\%. In this study, there was no statistically significant difference in the response rate to infliximab (\(p=0.42\)) between the 5 treatment regimens. The early infliximab treatment group had a shorter fever duration until infliximab infusion. We believe this is the reason that the early infliximab treatment group, who appeared to have a lower response rate than average, was associated with a more favorable CAA outcome as compared to that of the other subgroups. The incidences of CA lesions were relatively low in the infliximab group (9.1\% and 6.3\%, respectively) versus the additional IVIG group (12.5\% and 20.0\%, respectively), although a
statistically significant difference in the incidence of CA lesions was not observed. However, there is still controversy whether infliximab therapy improves coronary outcomes.

In our study, the incidence of significant CAA was lower in group 1 (early infliximab treatment without steroids) than in group 2 (1/42 [2.4%] vs. 17/60 [28.3%], p<0.001) possibly because of the longer fever duration until infliximab infusion in group 2 (16.4±4.5 days) than in group 1 (10.5±4.4 days). The response rate to infliximab treatment was not different for groups 1 and 2, but the CAA outcome was different. We assume, the late treatment group with steroid use developed more significant CAA because a patient’s responsiveness to infliximab treatment can be quickly determined, usually within 24 hours, as compared to confirming the responsiveness to a steroid treatment, which can require one dose, three consecutive doses, or further oral steroid tapering. Furukawa et al. suggested that IVMP is an effected additional therapy for IVIG-resistant KD, however, there was a tendency for the fever to recur later in IVMP-resistant patients. Although fever initially resolved faster in patients receiving IVMP, fever tended to be masked in most cases and recurred later in IVMP-resistant patients, which delayed therapeutic decision-making, resulting in CA lesions. This study suggests that early infliximab use, rather than the use of steroids, after IVIG treatment may be beneficial in preventing CA complications in patients with IVIG-resistant KD.

Although our survey data indicated more early infliximab use over the past 8 years as compared to a previous study, there was a tendency of late infliximab use in hospitals.

The most common symptoms of immediate infusion reactions have been flushing and shortness of breath. Complications of infliximab administration include the reactivation of latent tuberculosis and an increased risk of bacterial sepsis. Because infliximab is administered only once in most patients with refractory KD, its administration may cause fewer complications in KD patients than in patients with Crohn’s disease or juvenile idiopathic arthritis, where it is administered repeatedly. No infusion reactions or complications were noted in our study.

The immunosuppressive agent MTX has been occasionally used to treat IVIG-resistant KD; but to date, it has not been routinely recommended. In our study, we could not assess the benefit of MTX treatment due to the small number of cases.

The limitations of this study include its retrospective nature and the use of multiple different adjunctive therapies following first IVIG treatment failure. Different IVIG preparations were used at each center. Concomitant anti-inflammatory therapies administered to several patients made it difficult to assess the effects of infliximab. Additionally, we were unable to collect more detailed data regarding the absolute diameter or z-score of each CA before and after infliximab treatment. Finally, physicians might have been more likely to give pulse steroids rather than infliximab to sicker patients with increased inflammatory markers, thus, accounting for the less favorable outcomes in the group 2 patients.

In summary, this retrospective multicenter study suggests that infliximab was well tolerated and reduced fever duration and early infliximab use after IVIG treatment may be beneficial to prevent CA complications in patients with IVIG-resistant KD.

However, further prospective randomized studies with larger sample sizes may be needed to identify the most beneficial treatment regimen.
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