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Procalcitonin levels predicting the infliximab response of immunoglobulin resistant Kawasaki disease

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ABSTRACT

Objective: To search the predictive factors of infliximab resistance in intravenous immunoglobulin (IVIG)-resistant Kawasaki disease (KD) patients.

Study design.

Twenty-seven patients with KD who received infliximab after 4–5 g/kg of IVIG therapy from 2013 to 2015 were consecutively recruited in this study. They were divided into two groups: patients who responded to infliximab (infliximab-responsive group, n = 15) and patients who required additional therapy for the disease control (infliximab-resistant group, n = 12). We analyzed the clinical and laboratory parameters just before the infliximab treatment including serum levels of procalcitonin and cytokines with respect to the infliximab response.

Results: Serum procalcitonin concentration ($P = 0.017$), neutrophils to lymphocytes ratio ($P = 0.013$), and % neutrophils ($P = 0.004$) were higher, and serum sodium concentration ($P = 0.017$) was lower in infliximab-resistant group than those of infliximab-responsive group, respectively. Multivariate logistic regression analyses indicated that higher procalcitonin concentration (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.00–5.00, $P = 0.046$) and lower sodium levels (OR 0.64, 95% CI 0.32–1.00, $P = 0.047$), but not other variables, were associated with infliximab-resistance. Serum procalcitonin concentrations positively correlated with the serum levels of interleukin-6, soluble tumor necrosis factor receptor type 1 and type 2, respectively. Analyses of the receiver operating characteristic (ROC) curve showed that the cut-off value of procalcitonin 2.0 ng/ml had 58.3% of sensitivity and 93.3% of specificity. ROC analysis yielded an area under the curve (AUC) of 0.739 to predict infliximab-resistance.

Conclusion: Serum procalcitonin might be an effective biomarker to predict infliximab resistance in severe KD patients who are refractory to IVIG treatment.

1. Introduction

Kawasaki disease (KD) is an acute systemic vasculitis primarily affecting infants and young children [1]. KD is at present the most common cause of acquired heart disease among children in developed countries. Coronary arterial abnormality (CAA) is the most critical complication of KD and results in the aneurysmal formation leading to myocardial infarction later in life. High-dose intravenous immunoglobulin (IVIG) is the standard first-line therapy for KD to control inflammation and reduce the risk of CAAs [2]. However, 10–20% of patients fail to respond to IVIG therapy [3]. They show a persistent or recrudescent fever after a single or repeated IVIG infusion(s), and have an increased risk for developing CAAs [4]. The additional treatment for IVIG resistant patients mainly consists of corticosteroids, plasma

Abbreviations: AUC, area under the curve; CAA, coronary arterial abnormality; CI, confidence interval; IL, interleukin; IQR, interquartile range; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; OR, odds ratio; PE, plasma exchange; ROC, receiver operating characteristic; sTNFRs, soluble tumor necrosis factor receptors; TNF, tumor necrosis factor

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exchange (PE), and infliximab [1]. However, steroid therapy at the late stage of disease is a risk factor of developing or worsening CAAs [5,6]. PE is a choice of treatment for refractory KD patients, while the difficulty in blood access among infants and complications such as hemodynamic instability limits the facilities that can perform [7,8]. Infliximab is a safe, established adjunctive therapy for IVIG-resistant patients [9,10]. Approximately 10% of patients are refractory to both IVIG and infliximab, and often require an additional intervention of PE [11,12]. Because infliximab is usually administrated at the later stage of illness, early identification of infliximab resistance is of great importance to reduce CAAs. However, there are no biomarkers to predict infliximab resistance. Our aim was to create a clinical prediction model of infliximab responsiveness among IVIG refractory patients.

Procalcitonin is a biomarker for severe bacterial infection and sepsis [13]. The production of procalcitonin is induced by proinflammatory cytokines including interleukin-1 (IL-1), IL-2, IL-6 and tumor necrosis factor (TNF)-α [14]. Several studies reported the clinical utility of procalcitonin as a biomarker which indicates the disease severity of KD [15,16]. However, there remains no information of the procalcitonin levels concerning the infliximab resistance in patients with refractory KD.

In the present study, we studied clinical variables including the levels of procalcitonin and proinflammatory cytokines at the time of the administration of infliximab in IVIG-resistant KD patients. The clinical significance and biological role of procalcitonin were discussed for predicting infliximab resistance and the disease process of systemic vasculitis.

2. Materials and methods

2.1. Patients

A total of 32 KD patients were refractory to 4–5 g/kg of IVIG and treated in Kyushu University Hospital between January 2013 and December 2015. Two patients without measurement of procalcitonin levels were excluded. Since 3 IVIG non-responders received PE instead of infliximab, 27 patients received infliximab were enrolled for the study (Fig. 1). The diagnosis of KD was based on the diagnostic guidelines in Japan [17]. In principle, infliximab was administered within the first 9 days of illness. The additional therapy was started for patients who developed recrudescent or persistent fever above 37.5 °C at least 24 h after the end of infliximab infusion, and/or developed CAAs. We performed PE for the infliximab-resistant patients with persistent high-grade fever after infliximab infusion, whereas we administered additional IVIG for the remaining patients who showed partial response to infliximab treatment. Coronary artery was assessed by echocardiography as abnormal when any of the following conditions were met: z score ≥ 2.5, internal diameter ≥ 3 mm in children younger than 5 years, internal diameter greater than 1.5 times the size of an adjacent segment or obvious irregularity of the coronary artery lumen. This retrospective observational study was approved by the Institutional Review Board at Kyushu University Hospital (29-120).

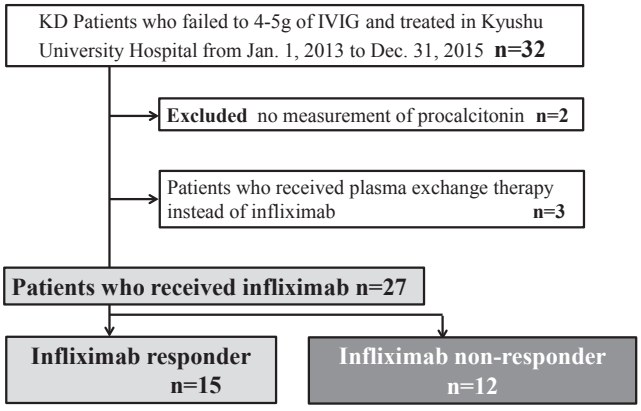

Fig. 1. Flowchart of the selection of 27 IVIG-resistant KD patients who received infliximab therapy. IVIG, intravenous immunoglobulin.

The medical records were reviewed to collect the demographic, laboratory and echocardiographic data, description of treatment, and outcome. Those patients who immediately responded to infliximab and required no additional therapy were defined as infliximab responders. In contrast, infliximab non-responders were those who received additional IVIG and/or PE due to persistent fever after infliximab infusion (Supplementary Fig. 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cyto.2018.11.025.

2.2. Measurement of serum procalcitonin and cytokines

Blood samples were collected from patients just before the infliximab therapy after written informed consents were obtained. Serum samples were separated from the peripheral blood by centrifugation, and were stored at −30 °C for the assays. Procalcitonin concentrations were measured by μTAS Wako i30 (Wako Pure Chemical Industries, Osaka, Japan). The serum concentrations of IL-6, IL-8, and soluble tumor necrosis factor receptors (sTNFRs) were measured by flow cytometry using EC800 cell analyzer (Sony Corporation, Tokyo, Japan) with a BD Cytometric Bead Array Human inflammatory cytokine kit (BD Biosciences, San Jose, CA, USA) for IL-6 and IL-8, and Human Soluble TNFR Flex Set (Bio-Techne, Minneapolis, MN, USA) for sTNFR1 and 2. The detection limits were 3.0 pg/ml for IL-6, 3.6 pg/ml for IL-8, 5.2 pg/ml for sTNFR1, and 1.4 pg/ml for sTNFR2, respectively.

2.3. Statistical analysis

Clinical variables were compared between infliximab responders and non-responders. Variables were analyzed by Student *t* test and Wilcoxon rank sum test for continuous and categorical variables, respectively, unless otherwise specified. Continuous variables were log transformed if their distribution significantly deviated from the normal. When the log-transformed value showed skewed distribution, Wilcoxon rank sum test instead of *t* test was used. Multivariate analyses with logistic regression were performed to determine the independent predictor of infliximab resistance. We selected laboratory variables which were scored with two points in Kobayashi score [18] as well as procalcitonin as variables for multivariate analysis. We evaluated the association between the predictors of infliximab resistance and the cytokines by calculating correlation coefficients. Receiver Operating Characteristics (ROC) was generated to find the best cut-offs for the predictors for infliximab resistance. A 2-sided P value of < 0.05 was considered statistically significant. Statistical analyses were performed using JMP Pro 13.2.0 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical profiles of the patients who underwent infliximab therapy

The study population consisted of 27 IVIG-resistant KD patients who thereafter received infliximab (Fig. 1). The median age at diagnosis was 3.0 (interquartile range [IQR] 1.8–4.5) years. There were 16 (59.3%) male patients. The median Kobayashi score was 6 (IQR 5–8) [18]. The number of infliximab responders and infliximab non-responders was 15 and 12, respectively. Of the 27 patients, 18 received IVIG twice, 4 received IVIG three times, and 5 received steroid therapy in addition to IVIG before infliximab therapy. Seven patients had CAAs at the time of infliximab therapy. The median days of infliximab treatment was 8 (range 7–16). Among 12 infliximab non-responders, 7 underwent PE. The remaining 5 infliximab-resistant patients experienced the

Table 1
Demographics and laboratory data at the IFX therapy in infliximab responders and non-responders.

	Infliximab responders		Infliximab non-responders nonnon-responders		*P*-value
	Value	n	Value	n	
Demographics					
Age (months)[b]	52 (17–62)	15	36 (28–41)	12	0.80
Male sex, n (%)	8 (53.3%)	15	8 (66.7%)	12	0.70
Days of illness at initial IVIG treatment[c]	4 (4–5)	15	4 (4–5)	12	0.65
Kobayashi score[c]	6 (5–8)	15	6 (5–8)	12	0.90
CAA at the time of infliximab therapy	3 (20.0%)	15	4 (33.3%)	12	0.66
Laboratory data at the time of infliximab therapy					
Leukocytes ($\times 10^9$/L)[b]	12.2 (10.0–13.6)	15	18.3 (8.8–24.0)	12	0.17
%Neutrophils[c]	68.5 (46.2–72.5)	15	80.7 (74.6–88.3)	12	0.004
Neutrophil to lymphocyte ratio[b]	3.3 (1.1–4.7)	15	6.6 (4.2–10.8)	12	0.013
Hemoglobin (g/dl)[a]	10.5 (9.9–11.1)	15	10.2 (9.5–10.9)	12	0.44
Platelets ($\times 10^9$/L)[b]	379.0 (317.0–517.0)	15	298.0 (233.5–486.0)	12	0.16
Albumin (g/dl)[a]	2.7 (2.4–2.9)	15	2.4 (2.1–2.7)	12	0.17
AST (U/L)[a]	34.8 (27.9–41.7)	15	40.9 (32.6–49.3)	12	0.23
ALT (U/L)[c]	21.0 (16.0–33.0)	15	30.0 (20.5–61.5)	12	0.12
Total bilirubin (mg/dl)[c]	0.40 (0.30–0.40)	15	0.30 (0.23–0.50)	12	0.67
Sodium (mmol/L)[a]	135.9 (134.5–137.2)	15	133.2 (131.3–135.1)	12	0.017
C-reactive protein (mg/dl)[c]	5.7 (4.3–12.4)	15	11.6 (3.9–18.1)	12	0.51
Ferritin (ng/ml)[b]	136.4 (83.2–189.9)	14	214.2 (88.1–296.3)	11	0.30
BNP (pg/ml)[c]	41.9 (23.3–53.7)	14	44.7 (14.8–87.6)	11	0.80
Procalcitonin (ng/ml)[b]	0.5 (0.1–1.0)	15	2.6 (0.5–13.8)	12	0.017
Cytokine levels at the time of infliximab therapy					
IL-6 (pg/ml)[b]	115 (24–1047)	7	339 (21–2147)	8	0.76
IL-8 (pg/ml)[b]	2103 (330–4488)	7	16 (0–238)	8	0.088
sTNFRI (pg/ml)[b]	1550 (629–2016)	8	1543 (854–5239)	9	0.67
sTNFRII (pg/ml)[b]	5653 (5082–8638)	8	8391 (4660–17238)	9	0.23

CAA, coronary artery abnormality; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNP, brain natriuretic peptide; IL, interleukin; TNFRI, soluble tumor necrosis factor receptor type 1; TNFRII, soluble tumor necrosis factor receptor type 2; CI, confidence interval; IQR, interquartile range.
[a] Data are expressed as mean (95%CI) and *t* test was used.
[b] Data are expressed as median (IQR) and log transformed value was used for *t* test.
[c] Data are expressed as median (IQR) and Wilcoxon rank sum test was used.

resolution of high-grade fever with decreased CRP levels, and were then successfully treated by additional IVIG without developing CAAs. Three patients had CAAs at one month after the onset of KD (Supplementary Fig. 1).

3.2. The comparison of the variables between infliximab responders and non-responders

Infliximab non-responder group had greater proportion of neutrophils (median 80.7%, IQR 74.6–88.3% *vs.* 68.5%, IQR 46.2–72.5%, $P = 0.004$), higher neutrophil to lymphocyte ratio (median 6.6, IQR 4.2–10.8 *vs.* 3.3, IQR 1.1–4.7, $P = 0.013$), higher procalcitonin levels (median 2.6 ng/ml, IQR 0.5–13.8 ng/ml *vs.* 0.5 ng/ml, IQR 0.1–1.0 ng/ml, $P = 0.017$), and lower sodium levels (mean 133.2 mmol/L, 95% confidence interval [CI] 131.3–135.1 mmol/L *vs.* 135.9 mmol/L, 95% CI 134.5–137.2 mmol/L, $P = 0.017$) compared with infliximab responder group at the time of infliximab therapy (Table 1). No other variables differed significantly between the two groups. A multivariate logistic regression analysis indicated that increased procalcitonin levels (odds ratio [OR] 1.48, 95% CI 1.00–5.00, $P = 0.046$) and decreased sodium levels (OR 0.64, 95% CI 0.32–1.00, $P = 0.047$) were independently associated with infliximab resistance (Table 2).

Table 2
Multivariate logistic regression analysis for the prediction of infliximab resistance.

	Odds ratio[a]	95% confidence interval	*P*-value
Procalcitonin	1.48	1.00–5.00	0.046
Sodium	0.64	0.32–1.00	0.047
AST	1.08	0.98–1.20	0.13
%Neutrophil	1.04	0.98–1.15	0.18

AST, aspartate aminotransferase.
[a] Odds ratio per one unit increase.

3.3. The cut-off levels of procalcitonin and sodium with respect to infliximab resistance

The ROC curve was generated to determine the best cut-off of procalcitonin and sodium levels for prediction of infliximab resistance. When the cut-off level of procalcitonin was set at 2 ng/ml, the sensitivity and specificity for the prediction of infliximab resistance was 58.3% and 93.3%, respectively (Fig. 2A). When the cut-off level of serum sodium levels was set at 133 mmol/L, the sensitivity and specificity for the prediction of infliximab resistance was 50.0% and 100.0%, respectively (Fig. 2C). ROC analysis yielded an AUC of 0.739 for procalcitonin and of 0.753 for serum sodium levels, respectively. We then calculated the sensitivity and specificity for prediction of infliximab-resistance by combination of procalcitonin and sodium with each cut-off value. The combination of procalcitonin and sodium slightly improved the sensitivity to 75%.

Fig. 2B and D show the procalcitonin and sodium levels in infliximab responders and non-responders, respectively. As shown in Supplementary Fig. 1, infliximab non-responders received additional IVIG or underwent PE. The procalcitonin levels were higher in those who underwent PE (closed circle) than in those who did not (open triangle) (median 3.93 ng/ml *vs.* 0.57 ng/ml, $P = 0.006$, Fig. 2B). Serum sodium levels did not differ between patients who underwent PE and those who did not (median 132.0 mmol/L *vs.* 135.0 mmol/L, $P = 0.06$, Fig. 2D).

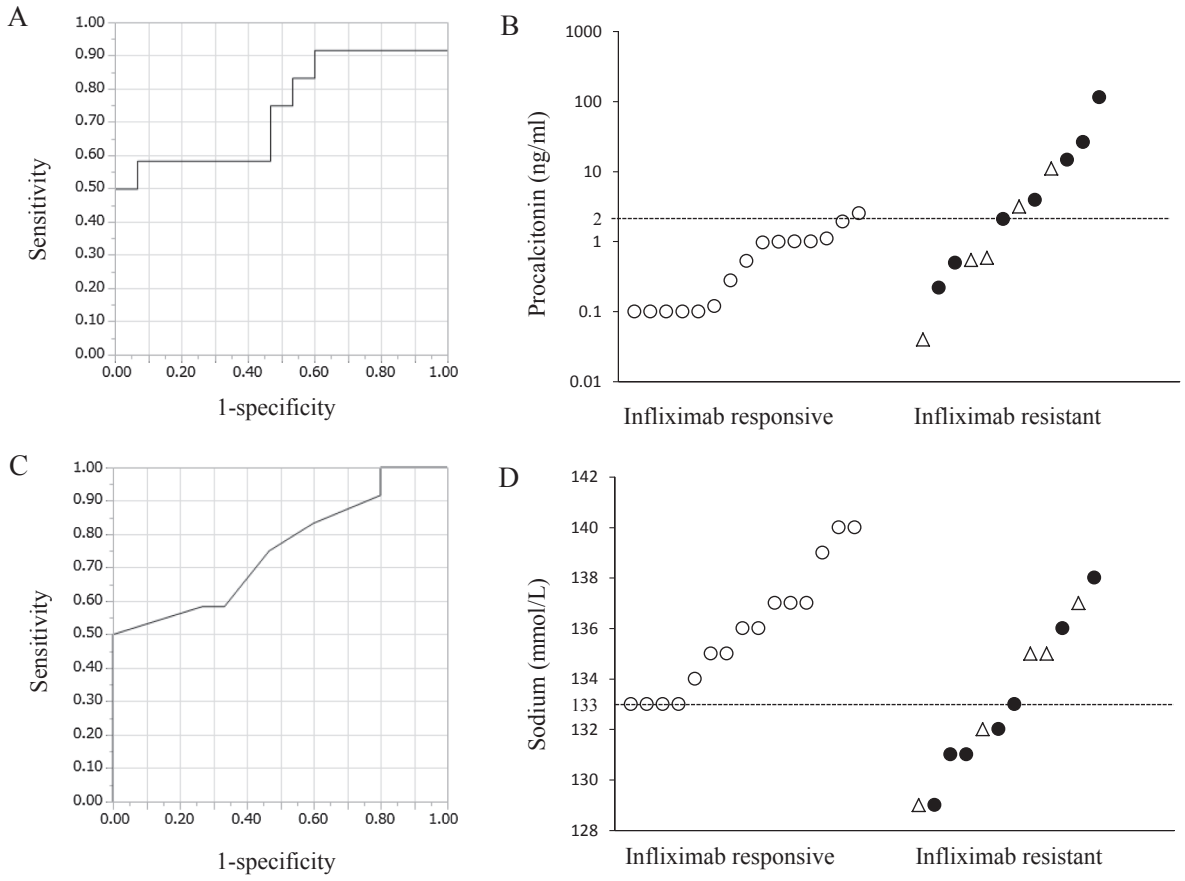

Fig. 2. Serum procalcitonin and sodium predict infliximab responsiveness. A and C) ROC curve for the serum procalcitonin (A) and sodium (C) levels with regard to infliximab responsiveness. The sensitivity and specificity for the prediction of infliximab resistance was 58.3% and 93.3% for procalcitonin at 2 ng/ml, and 50.0% and 100.0% for sodium at 133 mmol/L, respectively. (B) and (D) Serum procalcitonin (B) and sodium (D) levels in IVIG resistant KD patients who underwent infliximab treatment. Infliximab responders (open circle), non-responders who received additional plasma exchange (PE) therapy (closed circle) and non-responders who did not receive PE therapy (open triangle) are shown. Horizontal bars indicate the optimal cut-off values determined by the receiver operating characteristics curves in A and C.

3.4. The association between procalcitonin and inflammatory cytokines

Table 3 shows the association between procalcitonin, sodium and proinflammatory cytokines. The procalcitonin levels were associated with IL-6 (r = 0.61, $P = 0.016$), sTNFR1 (r = 0.77, $P = 0.001$) and sTNFR2 (r = 0.57, $P = 0.027$), respectively (Table 3). On the other hand, the serum sodium levels were not associated with these cytokines. IL-6, sTNFR1 and sTNFR2 correlated with each other. These cytokines were less effective than procalcitonin levels for predicting infliximab resistance assessed by ROC analysis (*data not shown*). Although IL-1β is the key inflammatory cytokine of KD and a major inducer of procalcitonin, the correlation was not analyzable because only two patients showed detectable levels of IL-1β in our subjects.

4. Discussion

We herein reported, for the first time, that high procalcitonin levels or low sodium levels independently predicted the resistance of infliximab therapy in patients with KD who were refractory to IVIG treatment. Notably, the procalcitonin levels showed a stronger correlation with the infliximab resistance than the inflammatory cytokine levels despite the significant association between these levels. When the cut-off level of procalcitonin was set at 2 ng/ml, the specificity for the infliximab resistance was as high as 93.3%. Patients with > 2 ng/ml of procalcitonin may require the intensive post-infliximab therapy including PE to control the severe inflammation.

TNF-α and IL-6 signaling pathways are activated in monocytes

Table 3
Correlations between procalcitonin, proinflammatory cytokines, and sodium among IVIG-resistant patients who underwent infliximab treatment.

	Procalcitonin		Sodium		IL-6		IL-8		sTNFRI		sTNFRII	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Procalcitonin			−0.15	0.47	**0.61**	**0.016**	−0.06	0.84	**0.62**	**0.007**	**0.7**	**0.002**
Sodium	−0.15	0.47			−0.049	0.86	0.51	0.065	−0.001	1	−0.14	0.59
IL-6	**0.61**	**0.016**	−0.049	0.86			0.52	0.057	**0.77**	**0.001**	**0.57**	**0.027**
IL-8	−0.06	0.84	0.51	0.065	0.52	0.057			0.38	0.18	−0.044	0.88
sTNFRI	**0.62**	**0.007**	−0.001	1	**0.77**	**0.001**	0.38	0.18			**0.75**	**0.001**
sTNFRII	**0.7**	**0.002**	−0.14	0.59	**0.57**	**0.027**	−0.044	0.88	**0.75**	**0.001**		

r, correlation coefficient; IL, interleukin; TNFRI, soluble tumor necrosis factor receptor type 1; TNFRII, soluble tumor necrosis factor receptor type 2.
P-value < 0.05 was considered significant, significant values are shown in bold.

obtained from patients during the acute phase of KD [19,20]. These proinflammatory cytokines are excessively released in the circulation of those who are resistant to IVIG therapy, and serum levels of TNF-α have been associated with the development of CAAs [21,22]. The cytokine profile reflects the magnitude of inflammation, but no single biomarker was found to predict the treatment response of refractory KD. Serum procalcitonin levels are widely used in practice for distinguishing bacterial infection from viral infection [23], although the precise source of the circulating molecule remains elusive. The procalcitonin levels also increase in cases of non-infectious conditions including surgery, burn, heart failure as well as vasculitis syndrome including KD [24–29]. Several proinflammatory cytokines including TNF-α and IL-6 are known to induce the production of procalcitonin [30]. In the present study, the positive correlation of procalcitonin levels with sTNFR1, sTNFR2 and IL-6 levels in IVIG-resistant KD patients might corroborate the severity of systemic vasculitis of patients with KD. In this setting, it may raise the possibility that the procalcitonin levels reflect the magnitude of uncontrolled inflammation at the time of the second-line therapy for refractory KD in association with monocyte activation.

The present study also revealed that serum sodium levels were the other independent predictor of infliximab resistance. IL-1 and IL-6 induce the inappropriate secretion of antidiuretic hormone. Vascular endothelial growth factors augment the hyperpermeability of arterial vessels. Increased circulating levels of IL-2, IL-6, and TNF-α might be associated with the mechanism of hyponatremia in KD patients [31]. However, in the present study, serum sodium levels were not as useful as procalcitonin levels for discriminating the infliximab non-responders who require additional PE treatment from those who did not. The absent correlation in the levels of sodium with IL-6 or TNF-α may further imply the distinct inflammatory process of refractory KD for predicting the treatment response.

CRP is also one of the important biomarkers for predicting IVIG responsiveness and CAAs [18,32]. However, we found no significant difference in the CRP levels between infliximab responders and non-responders. Serum concentrations of CRP peak at 36 h and fall with a half time of 48 h, while procalcitonin levels peak at 8 h and fall with a half time of 24–36 h [33–35]. The physiological production of CRP is under the dual control of IL-1 and IL-6, but not directly TNF-α [36]. The procalcitonin levels were significantly associated with TNF-α and IL-6 levels, the key cytokines of KD, in cases of initial IVIG-resistant KD in the present study. However, the CRP levels alone do not always reflect the severity of KD and/or the treatment response of IVIG. The present results of ROC analyses indicated the clinical utility of procalcitonin as a single biomarker that reflects the treatment response of patients with IVIG-resistant KD. Taken together, these emphasize the potential utility of procalcitonin levels as a single biomarker of infliximab resistance than CRP levels as well as the other combination of cytokine levels, partly based on the early elevation and shorter half time along with the involvement of TNF-α signaling pathway.

It remains a challenge to establish the treatment in IVIG-resistant KD patients whose procalcitonin levels are high. We reported that over 90% of those with > 2 ng/ml of procalcitonin received rescue treatment such as PE in addition to infliximab. Simultaneously, the significant correlation was determined among procalcitonin, IL-6 and TNF-α levels. High procalcitonin levels may reflect prominent hypercytokinemia accounting for uncontrollable inflammation even after a single infusion of infliximab.

There is little information about the mechanism of refractoriness to IVIG or infliximab during the prolonged treatment course of KD. Further studies are needed to determine whether high-dose or repeated administration of infliximab works in part of patients with refractory KD. Although most of the IVIG-resistant KD patients with high procalcitonin or low sodium levels were resistant to infliximab and required additional treatment, approximately half of the infliximab-resistant patients were then successfully treated with additional IVIG without developing CAAs. We consider that infliximab could be useful in these patients, whereas half of the remaining infliximab-resistant patients eventually required PE. Further study is mandatory for the early identification of these PE-requiring cases.

This study has several limitations. First, this study is a small retrospective study. Second, the treatment prior to infliximab varied between patients. Third, the rationale to pick up procalcitonin from two comparable laboratory markers was weak. Procalcitonin was higher in IVIG-resistant patients who underwent PE, whereas serum sodium levels did not differ between those who underwent PE and those who did not. Furthermore, procalcitonin, but not sodium levels, significantly correlated with IL-6 or sTNFR levels, the key cytokines in KD. Therefore, we considered that procalcitonin is a more useful marker than sodium to determine the treatment choice of refractory KD. Finally, even if procalcitonin could predict the necessity of PE, the superiority of PE compared with additional IVIG as a third-line treatment has not been established. Mori et al. [37] showed that patients who underwent PE therapy developed CAA less frequently than patients who received additional IVIG as a third line therapy. They also reported the lower persistent rate of CAA among PE group [37]. Infliximab and subsequent rescue with PE in IVIG-resistant KD patients suppressed the formation of CAA [38]. There is a case report supporting the superiority of PE over additional IVIG as a third- or fourth-line treatment [39]. We consider that PE would be the appropriate treatment for patients with persistent high-grade fever after infliximab infusion. Further prospective studies are warranted to better understand the efficacy of procalcitonin as a biomarker to predict the infliximab responsiveness.

5. Conclusion

Procalcitonin is a useful biomarker that helps to discriminate patients who eventually need additional treatments especially PE after infliximab treatment. Early identification of infliximab resistance leads to appropriate adjunctive therapy to prevent the development and progression of CAAs.

Conflict of interest statement

The authors declare no conflicts of interest.

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