Clinical Rheumatology (2019) 38:749–754
https://doi.org/10.1007/s10067-018-4339-0

ORIGINAL ARTICLE

IgG levels in Kawasaki disease and its association with clinical outcomes

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Received: 8 May 2018 / Revised: 30 September 2018 / Accepted: 12 October 2018 / Published online: 20 October 2018

Abstract

Previous studies have suggested an association of IgG levels (before and after IVIG infusion) with clinical outcomes in Kawasaki disease. A retrospective analysis was performed that included 418 patients with KD admitted to Tokyo Women's Medical University Yachiyo Medical Center to evaluate pre- and post-IVIG IgG levels and its relation to outcomes. All patients received an initial IVIG infusion and aspirin; IgG levels were measured in 350 patients before IVIG (pre-IVIG IgG levels) and in 373 patients 48 h after starting IVIG infusion (post-IVIG IgG levels). Media and standard deviation of the pre- and post-IVIG IgG levels were reported and classified according to age. Also, IgG z-scores were calculated according to normal values of IgG by age. The number of cases and corresponding percentage of non-responders were reported by age and total patients. The association of pre-IVIG, post-IVIG IgG levels and post-IVIG IgG level/pre-IVIG IgG level ratio with no-response was evaluated by simple logistic regression model based on the IgG z-score, and regression coefficient, X^2 value, p, and R^2 of Nagelkerke were reported. Pre-IVIG and post-IVIG IgG levels presented an association with non-responders with statistical significance. This association was more evident between post-IVIG IgG levels and non-responders. Regarding coronary alterations, it was not possible to perform an adequate statistical analysis due the small number of patients. Pre- and post-IVIG infusion IgG levels could be an important biomarker in KD as well as in other inflammatory conditions. Higher IgG levels could be associated with a more effective immunomodulatory action and associated with better clinical outcomes.

Keywords IgG · IgG levels · Intravenous immunoglobulins · Kawasaki disease

Introduction

In 1981, intravenous immunoglobulin (IVIG) was first used to treat a child with agammaglobulinemia and secondary immune thrombocytopenic purpura (ITP) [1]. High-dose IVIG was subsequently used to treat more children with ITP. Based on this study, Furusho et al. described IVIG in patients with Kawasaki disease (KD) using a similar protocol of 400 mg/kg daily for 5 days [2]. Lower doses of IVIG in KD were studied but only the highest dose showed a beneficial effect on coronary outcomes [3, 4]. Newburger et al. compared a single vs. four infusions of IVIG in Kawasaki disease (KD) and postulated a possible association between post-infusion IgG levels and the therapeutic response [5, 6]. Low IgG levels before IVIG administration have also been associated with coronary abnormalities [7]. In the present study, serum IgG levels before and after IVIG were analyzed in KD patients to investigate its relation to clinical outcomes.

Methods

A retrospective analysis was performed that included 418 patients with KD (typical and incomplete) admitted to Tokyo Women's Medical University Yachiyo Medical Center between January 2008 and June 2013. All patients received an initial IVIG infusion (2 g/kg for 24 h) and aspirin (50 mg/kg/day); IgG levels were measured in 350 patients before (pre-

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IVIG IgG levels) and in 375 patients 48 h after starting IVIG infusion (post-IVIG IgG levels). The definition of coronary artery abnormalities (CAAs) was based on the Japanese Ministry of Health diagnostic criteria (Research Committee on Kawasaki Disease. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Tokyo, Japan: Ministry of Health and Welfare, 1984 (in Japanese)) and consisted on measurements of the coronary artery internal diameter segment ≥ 3 mm in children < 5 years old or ≥ 4 mm in children ≥ 5 years old, an internal diameter of a segment ≥ 1.5 times that of an adjacent segment, an internal diameter of a segment ≥ 1.5 times that of the baseline, or if the coronary lumen was clearly irregular. We defined the patients with CAAs when they had CAAs at 1 month after the disease onset.

The patients were divided based on their response to IVIG treatment as responders and non-responders. The responder group included patients who received a single dose of IVIG (2 g/kg) and had no fever 48 h after IVIG, while the non-responder group included patients who received more than one dose of IVIG due to persistent or recurrent fever (second dose IVIG group). There was a subgroup of the non-responder patients that did not respond to the second IVIG dose and received a third-line treatment due to persistent or recurrent fever. These patients received cyclosporine A and/or a 3rd IVIG dose.

Statistical analysis

Media and standard deviation of the pre- and post-IVIG IgG levels were reported and classified according to age (1–3 months, 4–6 months, 7–11 months, 12–23 months, 24–35 months, 36–71 months, and > 72 months). To eliminate the effects of potential confounding by age, we transformed the serum IgG level with use of Z-score (standard deviation units) based on age-specific standard values for normal patients [8]. The number of cases and corresponding percentage of non-responders were reported by age and total patients. The association of pre-IVIG IgG levels, post-IVIG IgG levels, and post-IVIG IgG level/pre-IVIG IgG level ratio was evaluated by simple logistic regression model based on the IgG z-score, reporting regression coefficient, Wald χ^2 value, p value, and R^2 of Nagelkerke. To evaluate the prognostic capacity of pre- and post-IVIG treatment IgG levels to identify non-responders, optimal cutoff point of z-cores of IgG levels was determined by using ROC (receiver operating characteristics) curves and then parameters of predictive accuracy such as area under the curve (AUC), overall accuracy (OA), sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were estimated. The equivalent values of IgG in mg/dl for their z-shore were reported in each age group. Statistical significance was recognized as a level of $p < 0.05$. The estimated parameters were reported with a confidence interval of 95%. The statistical analysis was performed using JMP11 (SAS institute) and SPSS21 (IMB) statistical software.

Results

A total of 418 patients were included (243 male and 175 female), from 1 month of age to 11 years old; however, pre-IVIG IgG levels were available in 350 patients and post-IVIG IgG levels in 373. The number of non-responder patients is shown in Table 1, with 100 requiring a second dose of IVIG, 25 receiving cyclosporine, 16 a third dose of IVIG. Twenty-seven patients received a third IVIG dose and/or cyclosporine. The distribution by age of the patients is presented (Table 1). As expected, pre-IVIG IgG levels tended to present the physiological IgG levels curve, with the lowest levels between 4 and 6 months of age. Interestingly, children from 1 to 3 years old presented a lower IgG z-scores of IgG levels and this tendency is compatible with the frequency of non-responders. In all ages, pre-IVIG IgG levels were lower than expected but after IVIG administration, the IgG levels were high (Table 1).

With the exception of pre-IVIG IgG levels and the need of a third dose of IVIG, pre-IVIG and post-IVIG IgG levels presented statistically significant association with non-responders defined as cyclosporine required, third dose IVIG required, and third IVIG dose and/or cyclosporine required cases, whereas the post/pre-IVIG IgG ratio did not show such association. In all cases, the association between post-IVIG IgG levels and non-responders was strong compared with association of pre-IVIG IgG levels and non-responders (Table 2). Regarding coronary alterations, it was not possible to perform an adequate statistical analysis due the small number of patients with this complication.

In Table 3, the predictive utility of IgG converted to IgG z-score is summarized. By comparing AUC, post-IVIG IgG levels showed more predictive capacity for cyclosporine, a third IVIG dose and their composite. Regarding sensibility, post-IVIG IgG levels were always higher than pre-IVIG IgG levels; over 0.90 for all the criteria to identify non-responders, the specificity of pre-IVIG did not reach the same level. In general, post-IVIG IgG levels showed higher sensitivity than specificity, and vice versa tendency was observed with pre-IVIG IgG levels. Estimated LR+ and LR− values suggest that post-IVIG IgG levels could contribute to improve post-test probability to predict non-responders. Mean values of IgG concentration (mg/dl) and z-scores by age are presented in Table 4.

Discussion

IVIG is used in primary immunodeficiency diseases and in inflammatory or autoimmune disorders. In primary

Table 1 Pre- and post-IVIG treatment IgG level (mg/dL and Z score) of each age stratum and corresponding non-responder frequency (proportion)

Age group [month]	IgG PRE [mg/dL] mean (SD)	IgG POST [mg/dL] mean (SD)	IgG PRE [Z score] mean (SD)	IgG POST [Z score] mean (SD)	Non-responder criteria			
					2nd IVIG, *n* (%)	CsA, *n* (%)	3rd IVIG, *n* (%)	CsA and/or 3rd IVIG, *n* (%)
≥ 72 (*n* = 21)	870 (266)	3150 (525)	− 0.21 (1.04)	8.70 (2.05)	4 (17%)	0 (0%)	0 (0%)	0 (0%)
36–71 (*n* = 123)	812 (222)	2952 (486)	− 0.52 (0.97)	8.87 (2.13)	31 (25%)	8 (7%)	4 (3%)	8 (7%)
24–35 (*n* = 90)	729 (177)	2814 (319)	− 0.89 (0.97)	10.50 (1.74)	26 (29%)	4 (4%)	2 (2%)	5 (6%)
12–23 (*n* = 99)	640 (175)	2645 (369)	− 0.58 (0.84)	9.01 (1.77)	27 (27%)	12 (12%)	9 (9%)	12 (12%)
7–11 (*n* = 41)	475 (132)	2504 (398)	− 0.85 (0.60)	8.41 (1.82)	7 (17%)	1 (2%)	0 (0%)	1 (2%)
4–6 (*n* = 22)	375 (122)	2581 (474)	− 0.28 (0.65)	11.58 (2.55)	3 (11%)	0 (0%)	0 (0%)	0 (0%)
1–3 (*n* = 14)	416 (98)	2265 (243)	− 0.12 (0.82)	16.26 (2.04)	2 (14%)	0 (0%)	1 (7%)	0 (0%)
Global (*n* = 418)	–	–	− 0.60 (0.91)	9.60 (2.44)	100 (24%)	25 (6%)	16 (4%)	27 (6%)

IVIG intravenous immunoglobulin, *IgG PRE* pre IVIG treatment IgG level, *IgG POST* post-IVIG treatment IgG level, *CsA* cyclosporine

immunodeficiencies, IVIG is administered as replacement therapy, between 400 and 800 mg/kg/monthly and a higher trough IgG levels have been recommended. A meta-analysis showed that the pneumonia risk is progressively reduced by higher trough IgG levels (up to at least 1000 mg/dl) [9]. On the other hand, in autoimmune and inflammatory diseases the role of IgG levels has not been well characterized.

The efficacy of IVIG administered in the acute phase of KD is now well established, a variety of mechanisms of action have been attributed to IVIG. IVIG dose-dependent DC-mediated expansion of peripherally induced regulatory T cells (iTreg) has been reported in human cells, IVIG contains antibodies against sialic acid-binding immunoglobulin-like lectins (siglecs) expressed on the surface of neutrophils, and binding to these lectins can result in cell death [9]. In KD patients, enumeration of circulating NK cells pre- and post-IVIG demonstrated a rapid increase in the number of circulating NK cells that presumably represented the influx of demarginated cells bound to endothelium; other reported effects include modulation of T cell differentiation and cytokine release, increased T cell regulation, decreased proliferation of Th17 cells, and reduced cytokine release [10].

Lower total proteins (albumin and mainly IgG) have previously been associated with more severe inflammation, coronary artery lesions, and no-response to IVIG [11, 12]. Low IgG levels before IVIG treatment has been reported as a risk factor for coronary abnormalities; however, other studies have not corroborated this finding [7, 13]. In our study, we observed that pre-IVIG IgG levels correlated with IVIG resistance, with lower levels associated with the need of additional IVIG doses.

Table 2 Association of pre- and post-IVIG treatment IgG Z-score with non-responders

Y	*X*	*β* (SE)	χ^2	*p* value	Nagelkerke R^2
2nd IVIG required	IgG PRE	− 0.400 (0.159)	6.81	0.009	0.03
CsA required	IgG PRE	− 0.850 (0.356)	6.45	0.011	0.06
	IgG POST	− 0.630 (0.153)	22.24	< 0.001	0.15
	IgG POST/PRE	0.077 (0.145)	0.26	0.607	< 0.01
3rd IVIG required	IgG PRE	− 0.636 (0.414)	2.60	0.107	0.03
	IgG POST	− 0.699 (0.196)	16.62	< 0.001	0.19
	IgG POST/PRE	− 0.111 (0.234)	0.251	0.616	< 0.01
CsA and/or 3rd IVIG required	IgG PRE	− 0.759 (0.339)	5.60	0.018	0.04
	IgG POST	− 0.618 (0.148)	22.64	< 0.001	0.18
	IgG POST/PRE	0.039 (0.149)	0.07	0.798	< 0.01
AC	IgG PRE	− 0.011 (0.635)	< 0.01	0.987	< 0.01
	IgG POST	− 0.072 (0.222)	0.11	0.738	< 0.01
	IgG POST/PRE	− 0.937 (0.802)	2.06	0.151	0.06

IVIG intravenous immunoglobulin, *CsA* cyclosporine, *IgG PRE* pre IVIG treatment IgG level [Z score], *IgG POST* post-IVIG treatment IgG level [Z score], *IgG PRE/POST* the ratio of IgG POST versus PRE

Table 3 Predictive utility of pre- and post-IVIG treatment IgG for non-responders by different criteria

Y	Predictor	COP	AUC	OA	Sensitivity	Specificity	RL+	RL−
2nd IVIG	IgG PRE	0.359	0.58 [0.51, 0.65]	0.34 [0.29, 0.39]	0.96 [0.92, 1.00]	0.17 [0.13, 0.22]	1.16 [1.08, 1.25]	0.23 [0.07, 0.72]
CsA	IgG PRE	− 1.355	0.70 [0.56, 0.83]	0.80 [0.76, 0.84]	0.60 [0.35, 0.85]	0.81 [0.77, 0.85]	3.14 [1.97, 5.02]	0.49 [0.27, 0.92]
	IgG POST	8.787	0.81 [0.73, 0.89]	0.62 [0.57, 0.67]	0.94 [0.84, 1.00]	0.60 [0.55, 0.65]	2.36 [1.99, 2.80]	0.09 [0.01, 0.62]
3rd IVIG	IgG PRE	− 1.483	0.66 [0.50, 0.81]	0.85 [0.81, 0.89]	0.50 [0.19, 0.81]	0.86 [0.83, 0.90]	3.62 [1.84, 7.10]	0.58 [0.31, 1.08]
	IgG POST	8.612	0.84 [0.76, 0.92]	0.63 [0.59, 0.68]	0.91 [0.74, 1.00]	0.63 [0.58, 0.68]	2.44 [1.94, 3.07]	0.15 [0.02, 0.94]
CsA and/or 3rd IVIG	IgG PRE	− 1.355	0.68 [0.54, 0.81]	0.80 [0.76, 0.84]	0.56 [0.32, 0.81]	0.81 [0.77, 0.85]	2.94 [1.81, 4.77]	0.54 [0.31, 0.95]
	IgG POST	8.787	0.81 [0.73, 0.88]	0.62 [0.57, 0.67]	0.95 [0.85, 1.00]	0.60 [0.55, 0.65]	2.38 [2.01, 2.81]	0.09 [0.01, 0.59]

COP cutoff point determined by ROC curve, *AUC* area under curve, *OA* overall accuracy, *RL+* positive likelihood ratio, *RL−* negative likelihood ratio, *IVIG* intravenous immunoglobulin, *CsA* cyclosporine, *IgG PRE* pre-IVIG treatment IgG level [Z score], *IgG POST* post-IVIG treatment IgG level [Z score], *IgG PRE/POST* the ratio of IgG POST versus PRE

A variety of dose regimens were initially used in Japan and the USA. A meta-analysis by Durongpisitkul demonstrated that the prevalence of coronary artery abnormalities was lower among patients who received the high-dose regimen of 2 g/kg as a single dose as compared to those receiving lower-dose regimens [14]. It remains unknown whether the presumed higher peak level or its earlier administration was the reason for the superior efficacy of the single high-dose regimen; this important meta-analysis helped to settle the debate about optimal dose of IVIG in KD and suggested a dose–response threshold. The dose–response effect of IVIG on the incidence of coronary aneurysms also forms the basis for current practice of IVIG retreatment in KD patients with recrudescent or persistent fever [15].

In 1986, Newburger et al. demonstrated that high-dose IVIG is effective in reducing the prevalence of coronary artery abnormalities, children with and without coronary artery abnormalities who were treated with IVIG had comparable serum IgG levels at 5 days and 2 weeks. Five years later, in another study, Newburger et al. investigated the relation of age-adjusted serum IgG levels to the development of coronary artery abnormalities and the systemic inflammatory response. IgG on day 4 was a strong predictor of clinical outcomes, patients with lower concentrations had a higher prevalence of coronary artery abnormalities, a higher temperature on day 3, longer duration of fever and greater inflammation. Morikawa et al. also found that lower IgG level after IVIG infusion was a risk factor to develop coronary artery abnormalities; in our study, although we did not find a relation to develop coronary artery abnormalities probably due to the small number of patients with coronary alterations, we found an association of lower levels of IgG and the need to administer a second and a third dose of IVIG [16, 17]. Han et al. studied serum IgG levels in KD patients at discharge when inflammation was resolved, and hypothesized that the elevation of IgG observed might be involved in actions of repair as part of host immune/repair system in a network of a protein homeostasis system [18, 19]. Newburger et al. reported that children with coronary abnormalities had higher adjusted serum IgG levels at weeks 2 and 7, and the authors concluded that it was a result of continued polyclonal B cell activation [5, 6].

In our study, we investigated the serum IgG levels only at 48 h after starting IVIG infusion to explore its relation to the

Table 4 Age group specific cutoff point value of pre- and post-IVIG treatment IgG corresponding to Z-score to predict non-responders

Y	Predictor	Z-score	Age group (month)						
			1–3	4–6	7–11	12–23	24–35	36–71	72–
2nd IVIG	IgG PRE	0.359	473	494	740	837	958	1011	1015
CsA	IgG PRE	− 1.355	269	175	364	479	644	620	576
	IgG POST	8.787	1476	2061	2585	2598	2500	2932	3172
3rd IVIG	IgG PRE	− 1.483	254	151	336	452	621	591	543
	IgG POST	8.612	1455	2029	2547	2562	2468	2893	3128
CsA and/or 3rd IVIG	IgG PRE	− 1.355	269	175	364	479	644	620	576
	IgG POST	8.787	1476	2061	2585	2598	2500	2932	3172

IVIG intravenous immunoglobulin, *CsA* cyclosporine, *IgG PRE* pre-IVIG treatment IgG level [Z score], *IgG POST* post-IVIG treatment IgG level [Z score], *IgG PRE/POST* the ratio of IgG POST versus PRE

clinical efficacy of the IVIG. Our results suggest that both low pre-IVIG and post-IVIG IgG levels are associated with non-responsiveness, particularly the post-IgG levels. Higher post-IVIG IgG levels are associated with a better response. Cutoff values of post-IVIG-IgG levels according to age were calculated and shown in Table 4.

High IVIG doses have been recommended in several autoimmune diseases to achieve immunomodulatory effects. In Guillain–Barre syndrome (GBS), patients with low IgG 2 weeks after IVIG had a slower recovery and fewer reached the ability to walk unaided at 6 months [20]. Kuitwaard et al. showed that GBS patients show a large variation in pharmacokinetics and suggest that low IgG patients may benefit from higher doses or repeated doses of IVIG [20]. IVIG is also an effective treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); in this disease, a high serum IgG peak levels are required to induce a clinical response and to reach and maintain a stable clinical condition when treated with IVIG [21]. Subcutaneous immunoglobulin has been used in several neuroimmune diseases but we believe it does not have a role in the treatment of KD due to the fact that an adequate IgG level peak would not be achieved.

Variation in IgG levels may depend on the activity of the disease, immunological host factors, baseline IgG levels, IgG glycosylation, and Fc receptor polymorphisms. Other relevant factor that could be involved is the increased vascular leakage observed in severe KD patients generating lower IgG levels. Increased microvascular permeability with hypoalbuminemia has been reported as a key feature of KD pathophysiology [22]. Hypoalbuminemia has been associated with severe KD, coronary artery dilatation, and no-response to IVIG. In our study, there was a correlation between albumin levels and IgG levels post-IVIG (there was a positive correlation of 0.34 (95% CI 0.25, 0.43) (Pearson correlation coefficient $p < 0.001$) between albumin and IgG levels after IVIG infusion), and then an increased vascular leakage of IgG with less than optimal IgG levels may play a role in refractory cases.

Several limitations of the present study should be addressed. First, the number of patients with coronary abnormalities was small. Second, the retrospective nature of the study and finally, the information comes from a single center.

In conclusion, IgG levels at pre- and post-IVIG infusion could be an important biomarker in KD as well as in other inflammatory conditions. Higher IgG levels could be associated with a more effective immunomodulatory action and associated with better clinical outcomes. More studies are needed to corroborate our findings.

Compliance with ethical standards

Conflict of interest Dr. Marco Yamazaki-Nakashimada declares having received lecture fees from Octapharma, CSL Behring and Shire; the other authors declare not having any conflict of interest.

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