

Intravenous immunoglobulin preparation type: Association with outcomes for patients with acute Kawasaki disease

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To determine whether two different intravenous immunoglobulin (IVIG) preparations were equally efficacious in the treatment of Kawasaki disease (KD). Single centre retrospective review of all patients treated with IVIG for KD between January 1990 and April 2007. Comparison of IVIG (dose 2 g/kg) from two commercial preparations; Iveegam[®] stabilized with sugar (lyophilized, 5 g/ml glucose, pH 6.4–7.2, IgA 10 µg/ml, 5% IgG/ml) and Gamimune[®] stabilized through acidification (no sugar, pH 4.0–4.5, IgA 270 µg/ml, 5% 1990–1999, 10% 1999–2007 IgG/ml). Propensity-adjusted differences in duration of fever after treatment initiation, frequency of retreatment with IVIG, hospital stay and maximum coronary artery z-score. A total of 954 patients were included, 862 (90%) were treated with Iveegam[®] and 92 (10%) were treated with Gamimune[®]. Patients' demographic, clinical and laboratory characteristics were similar between the two groups. In propensity-adjusted models, Iveegam[®] was found to be associated with higher probability of non-response to IVIG (12% vs. 5%, $p = 0.05$) and longer median duration of fever after IVIG [1 (1–27) vs. 1 (1–8) days, $p = 0.02$] than Gamimune[®]. Nevertheless, Gamimune[®] was found to be associated with longer median duration of hospital stay [5 (2–49) vs. 4 (2–76) days, $p < 0.0001$] and higher median maximum coronary artery z-score both at the end of the acute phase (+1.4 vs. +0.8, $p < 0.0001$) and 6–8 weeks after the acute phase (+0.7 vs. +0.4, $p < 0.0001$). IVIG preparations with lower IgA content and stabilized with glucose appear to be associated with improved coronary artery outcomes for patients with KD.

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High-dose intravenous immunoglobulin (IVIG) is the mainstay of therapy for children in the acute phase of Kawasaki Disease (KD), an acute pediatric vasculitis, potentially leading to the formation of coronary artery aneurysms (1). It is widely recognized that longer duration of active disease is a potent risk factor for the development of coronary artery abnormalities, and as such the goal of treatment in the acute phase of KD is to stop the inflammation as soon as possible (2). IVIG is a powerful suppressor of inflammation and its use has been shown to reduce the

prevalence of severe coronary artery abnormalities because of KD from 20% to 25% in untreated patients to <5% (3–5).

Commercially available IVIG preparations differ widely in production, purification, IgA content and, especially, stabilization processes. This has led to variability in the pharmacological and biochemical properties (6). While IVIG in general has been shown to be highly effective and safe, studies have shown, both in the KD population and with other illnesses, that differences in efficacy (7,8) and safety (9,10) exist between different

preparations. Differences in efficacy are particularly worrisome in the context of KD as treatment is time sensitive and non-response is associated with a high risk of developing coronary artery abnormalities (11). To date, only a handful of studies have explored the differences in efficacy and safety between preparations in the context of KD (7, 10, 12–14), and none have adequately adjusted for potential confounding in treatment choice. We sought to compare the efficacy, in terms of defervescence, duration of hospital stay and coronary artery outcomes, of two different commercial preparations of IVIG commonly used in the treatment of KD.

Methods

Medical records of all patients with KD seen at The Hospital for Sick Children, Toronto, between January 1990 and April 2007 were reviewed. The study was approved by the Hospital's Research Ethics Board, and the requirement for individual consent was waived for a retrospective study. As per current guidelines, complete KD presentation was defined as fever ≥ 5 days duration and at least four out of the following clinical signs: bilateral conjunctival injection, cervical lymphadenopathy, polymorphous skin rash, changes in the lips or oral mucosa, and changes of the extremities. Incomplete KD was defined as fever ≥ 5 days duration and 2–3 of the above named clinical signs. Patients with either type of presentation were included in this study.

During this period, patients with a diagnosis of KD received one of two IVIG preparations: Iivegam EN[®] (0704509; Baxter Healthcare Corporation, BioScience Division, Deerfield IL, USA) stabilized with sugar (lyophilized, 5 g/ml glucose, pH 6.4–7.2, IgA 10 μ g/ml, 5% IgG/ml) or Gamimune N[®] (08692249; Bayer Health Care, Biologic Product Division, Research Triangle Park, NC, USA) stabilized through acidification (no glucose, pH 4.0–4.5, IgA 270 μ g/ml, 5% between 1990 and 1999, 10% between 1999 and 2007 IgG/ml). As per institutional protocol Iivegam[®] was favored for this population when available. Both preparations were generally available throughout the entire study period; however, shortages of specific brands did happen sporadically. Complete pharmacological characteristics of both preparations are provided in Table 1. The treatment regimen was standardized regardless of IVIG preparations and consisted of IVIG 2 g/kg, in a single continuous infusion with a predetermined infusion rate, and aspirin. All children diagnosed with KD at The

Hospital for Sick Children underwent a standardized KD assessment at diagnosis, which included medical history, physical examination, cardiac assessment, laboratory testing, electrocardiogram and echocardiogram. Data abstracted from medical records included patients' demographics, clinical presentation, laboratory investigations (last measurement prior to IVIG infusion), medical management, response to treatment and coronary artery outcomes.

Patients were considered afebrile when their temperature dropped below 37.5°C. Non-response to treatment was defined as fever persisting for at least 36 h after starting the initial IVIG infusion. Number of days from the start of the initial IVIG infusion to defervescence was recorded for each patient along with total duration of hospitalization.

Patients were defined as having coronary artery abnormalities as a result of KD if they met either the Japanese Ministry of Health criteria or if any coronary artery segment had a z -score ≥ 2.5 adjusted for body surface area (BSA) (1, 2). The Japanese Ministry of Health defines coronary artery abnormalities as any coronary segment ≥ 3 mm in children < 5 yr old and ≥ 4 mm in children ≥ 5 yr old, or if the internal diameter of any segment was ≥ 1.5 times greater than any adjacent segment (2). Coronary artery abnormalities ≥ 5 mm regardless of age and/or those with BSA-adjusted z -score ≥ 5 were classified as aneurysms. Maximum coronary artery z -score was taken as the highest coronary artery z -score out of the right main coronary artery, the left main coronary artery or the left anterior descending coronary artery. Patient status regarding coronary artery abnormalities was assessed at the end of the acute phase and was later confirmed

Table 1. Comparison of pharmacological and biochemical properties of Iivegam[®] and Gamimune[®]

	Iivegam [®]	Gamimune [®]
Distributor	Baxter Corporation Bio Science Division	Bayer Health Care Biologic Products Division
Method of production	Cold ethanol fraction Phosphoethylene glycol Trypsin treatment	Cold ethanol fraction Phosphoethylene glycol Diafiltration/acidification
Concentration	5% IgG/ml	5% IgG/ml (1990–99) 10% IgG/ml (1999–2007)
Immunoglobulin A	10 μ g/ml	270 μ g/ml
Time to infuse 24 g*	11.3 h	11.3 h (at 5% IgG/ml) 5.7 h (at 10% IgG/ml)
Osmolality	≥ 240 mOsm/l	274 mOsm/l
pH	6.4–7.2	4.0–4.5
Sugar content	5 g/ml glucose	None

IgG, Immunoglobulin G; ml, milliliters; kg, kilograms; h, hours; mOsm, milliosmole; l, liters; g, grams.

*Total IVIG required for a 12 kg infant at a 2 g/kg dose of IVIG.

in cardiology clinic follow-up 6–8 weeks after the acute phase.

Data are reported as means with standard deviations, medians with minimum and maximum values and frequencies as appropriate. Differences in patient demographics, clinical characteristics, medical management, response to treatment and coronary artery outcomes between IVIG preparations were first compared using Fisher's exact chi-square and Student's *t*-test with Satterthwaite correction to estimate variance. In order to provide some adjustment for non-randomized assignment of IVIG preparations, a propensity score was created. The score was calculated from a multivariable logistic regression model including all demographic, clinical and laboratory features associated with a statistical significant difference in probability of receiving one preparation vs. the other. This propensity score was included as a covariate in multivariable linear regression models examining the association between IVIG preparations and duration of fever after IVIG initiation, duration of hospital stay and maximum coronary artery *z*-score at the end of the acute phase and at the 6–8 weeks cardiology clinic follow-up. The propensity score was also included as a covariate in multivariable logistic regression models examin-

ing the association between IVIG preparations and non-response to IVIG and coronary artery abnormalities as previously defined. All statistical analyses were carried out using SAS v9.1 (The SAS Institute, Cary, NC, USA).

Results

From January 1990 to April 2007, 1374 children with KD were seen at The Hospital for Sick Children. Of those, 268 (20%) lacked information about the specific IVIG preparation used and 152 (11%) were never treated with IVIG for various reasons. Of the remaining 954 patients (592 males, 62%), 862 (90%) were treated with Iveegam® and 92 (10%) were treated with Gamimune®. With few exceptions, patients' demographic, clinical and pre-IVIG laboratory characteristics were similar between the two groups (Table 2). Patients who received Iveegam® were found to be less likely to have been initially hospitalized at external hospitals, had shorter duration of symptoms prior to diagnosis and had lower white blood cell count. These three variables were included in the propensity score used for subsequent adjustment.

A comparable proportion of patients were treated with aspirin (99% for both preparations)

Table 2. Demographic, clinical and laboratory features of Kawasaki disease patients comparing patients treated with Iveegam® to those treated with Gamimune®

	Iveegam®		Gamimune®		p
	[n]	(n = 862)	[n]	(n = 92)	
Demographics					
Sex (male)		542 (63%)		50 (54%)	0.12
Age at diagnosis (yr)		2.9 (0.2–17.7)		2.7 (0.2–14.2)	0.28
Diagnosed and treated at HSC		777 (90%)		74 (80%)	0.008
Delay symptoms onset-diagnosis (days)	[848]	6 (3–31)	[91]	5 (2–22)	0.08
Kawasaki disease clinical signs					
Incomplete presentation	[857]	180 (21%)	[91]	14 (15%)	0.22
Bilateral conjunctival injection	[847]	776 (92%)	[91]	95 (86%)	0.43
Cervical lymphadenopathy	[847]	556 (66%)	[91]	60 (66%)	1.00
Lips/oral mucosa changes	[847]	767 (91%)	[91]	80 (88%)	0.46
Polymorphous skin rash	[847]	748 (88%)	[91]	84 (92%)	0.30
Extremity changes	[847]	654 (77%)	[91]	65 (71%)	0.25
Laboratory investigations (prior to IVIG)					
Albumin (g/l)	[784]	36 ± 6	[79]	35 ± 6	0.28
Alanine transaminase (U/l)	[806]	27 (3–2483)	[54]	26 (3–449)	0.39
Aspartate transaminase (U/l)	[781]	36 (9–1000)	[55]	26 (10–50)	0.17
C-reactive protein (mg/l)	[650]	33 (10–387)	[14]	32 (24–109)	0.22
Erythrocytes sedimentation rate (mm/h)	[809]	71 ± 33	[83]	64 ± 35	0.11
Hematocrit	[838]	0.332 ± 0.035	[90]	0.328 ± 0.038	0.30
Hemoglobin (g/l)	[847]	112 ± 12	[91]	111 ± 13	0.36
Lymphocytes (×10 ⁹ /l)	[838]	2.6 (0.1–14.5)	[90]	2.6 (0.1–13.2)	0.90
Platelet (×10 ⁹ /l)	[845]	344 (60–6120)	[91]	406 ± 185	0.29
Red blood cells (×10 ¹² /l)	[667]	4.2 ± 0.5	[15]	4.1 ± 0.5	0.27
White blood cells (×10 ⁹ /l)	[844]	13.8 ± 6.1	[89]	15.3 ± 7.6	0.09

Mg, milligrams; g, grams; l, liters; mm, millimeters; U, unit; h, hour.

Table 3. Response to treatment and disease outcomes of patients with Kawasaki disease comparing patients treated with Iiveegam[®] to those treated with Gamimune[®]

	Iiveegam [®]		Gamimune [®]		p
	[n]	(n = 862)	[n]	(n = 92)	
Response to treatment and retreatment					
Non-response to initial IVIG*		100 (12%)		5 (5%)	0.08
Duration of fever after IVIG start (days)	[852]	1 (1–27)	[91]	1 (1–8)	0.02
Multiple IVIG doses		101 (12%)		4 (4%)	0.04
Steroids (any indications)		48 (5%)		3 (3%)	0.17
Hospitalization					
Hospital stay (days)	[848]	4 (2–76)	[91]	5 (2–49)	0.02
Coronary artery dimensions					
Maximum z-score end acute phase	[741]	+0.8 (–1.7 to +27.0)	[54]	+1.4 (–0.7 to +27.5)	0.02
Maximum z-score at 6–8 weeks	[772]	+0.4 (–2.4 to +39.0)	[66]	+0.7 (–1.0 to +34.4)	0.09
Coronary artery outcomes					
No coronary artery abnormalities		703 (82%)		73 (79%)	0.58
Coronary artery dilation only		125 (15%)		12 (13%)	0.88
Coronary artery aneurysms		34 (4%)		7 (8%)	0.11

Reported are medians with minimum and maximum values and frequencies.

IVIG, Intravenous immunoglobulin; RCA, Right coronary artery; LCA, Left main coronary artery; LAD, Left anterior descending coronary artery.

*Fever persisting for at least 36 h after starting the initial IVIG infusion.

Table 4. Unadjusted and propensity-adjusted comparisons of the association between individual disease outcomes and IVIG preparations

	Unadjusted		Propensity-adjusted	
	EST (s.e.)	p	EST (s.e.)	p
Non-response to IVIG*	0.826 (0.472)	0.08	0.943 (0.480)	0.05
Duration of fever after IVIG start (days)	0.191 (0.100)	0.06	0.236 (0.102)	0.02
Hospital stay (days)	–0.314 (0.045)	<0.0001	–0.299 (0.046)	<0.0001
Maximum z-score at baseline	–0.308 (0.049)	<0.0001	–0.286 (0.051)	<0.0001
Maximum z-score at 6–8 weeks	–0.194 (0.048)	<0.0001	–0.183 (0.050)	0.0002
Coronary artery aneurysms	–0.696 (0.430)	0.11	–0.727 (0.440)	0.10

Reported is the parameter estimates and standard error from bivariable logistic (non-response to IVIG, coronary artery abnormalities and coronary artery aneurysms) and bivariable linear (days of fever after IVIG, duration of hospital stay and maximum coronary artery z-score at baseline and 6–8 weeks) regression models for Iiveegam[®] vs. Gamimune[®].

EST, estimate; s.e., standard error; p, p-value; IVIG, intravenous immunoglobulin.

*Fever persisting for at least 36 h after starting the initial IVIG infusion.

and with antibiotics (46% Iiveegam[®] vs. 49% Gamimune[®], $p = 0.59$). Differences in response to treatment, requirements for retreatment and duration of hospital stay and coronary artery outcomes between preparations in unadjusted analysis are detailed in Table 3. In unadjusted comparisons, patients treated with Iiveegam[®] were found to be more likely to require a second IVIG dose and had longer duration of fever after initiation of IVIG treatment. On the other hand, patients treated with Gamimune[®] had a longer duration of hospital stay and higher maximum coronary artery z-score at the end of the acute phase.

Association between IVIG preparations and disease outcomes, both in unadjusted and in propensity-adjusted analyses, are detailed in Table 4. In propensity-adjusted models, Iiveegam[®] was found to be associated with higher

probability of non-response to IVIG and higher number of days of fever after the start of the initial IVIG infusion than Gamimune[®]. Gamimune[®] was found to be associated with longer duration of hospital stay and higher maximum coronary artery z-score, both at baseline and 6–8 weeks after the acute phase.

Discussion

This study supports the hypothesis that outcomes after KD might be associated with IVIG preparations. We found that Gamimune[®] was associated with significantly worse coronary artery outcomes at the end of the acute phase and at 6–8 weeks follow-up than treatment with Iiveegam[®] even when adjusting for potential confounding. This is potentially of clinical relevance as coronary artery abnormalities after KD

are associated with a high risk of stenotic occlusions (15), thrombus formation and myocardial infarction later in life (16). These children might require life-long anticoagulation (17) and surgical interventions (18). Even in children with only minimal coronary artery involvement, recent studies have shown persistent vascular dysfunction and the potential for an accelerated atherosclerotic process (19, 20).

Patients in both groups had similar demographic and clinical characteristics, and the finding that Gamimune[®] was more likely to be prescribed at external hospitals is not surprising as Iveegam[®] has been historically favored by our institution. With adjustments for potential confounding patient characteristics, using a propensity score, we are confident that both groups are comparable.

Iveegam[®] is available at a 5% concentration, while Gamimune[®] has been provided at a 10% concentration since 1999 (provided at a 5% concentration from 1990 to 1998). Consequently, the infusion volume required for an equivalent dose of IVIG is twice as great with Iveegam[®] than with Gamimune[®]. As a result, the time required to infuse a similar quantity of IgG protein is longer with Iveegam[®] than Gamimune[®] (11.3 hours vs. 5.7 hours). This probably explains why the duration of fever after IVIG infusion was longer and non-response to IVIG (assessed 36 h after the start of the infusion) was more frequent with Iveegam[®] than with Gamimune[®].

In a previous study by Tsai et al. (7), differences in efficacy in preventing coronary artery abnormalities were noted and attributed to the use of propiolactone and plasmin digestion. This affects the structure and function of the constant region (Fc) of the IgG molecule even if they do not affect the specificity of the variable region responsible to specific antibody binding (21, 22). The authors suggested that IVIG preparations which are manufactured through chemical or enzymatic processes that affect the Fc portion of the IgG molecule could be less effective. As the Fc portion of the immunoglobulin G molecule is thought to have an active therapeutic role in KD (23, 24) this potentially accounts for the higher rate of coronary artery abnormalities observed with those specific preparations. This manufacturing process is likely not the explanation behind the observation in our current study, showing that treatment with Gamimune[®] when compared to Iveegam[®] resulted in higher coronary artery z-score at the end of the acute phase and at 6–8 weeks follow-up. Firstly, in Tsai et al. (7), Gamimune[®]

performed better than other preparations, and secondly, Gamimune[®] is not treated with processes known to affect the constant portion of the immunoglobulin G molecule. The difference observed between the two preparations in this case could be explained by the differences in stabilization methods or IgA content. While Iveegam[®] is stabilized using glucose, Gamimune[®] is stabilized using acidification, thus resulting in marked differences in pH between the preparations. The infusion of a high volume of low-pH solution results in acidification of blood, and acidosis has been shown to cause a reduction in intracellular tone and a transient rise in tension (25–27). In the active phase of KD, vascular walls are known to be weakened because of inflammation and elastin degradation (28–30). Therefore, we do speculate that the physiologic changes associated with blood acidification could contribute to coronary artery dilation. This would explain why, while more effective in inducing defervescence and stopping inflammation, Gamimune[®] was found to be associated with higher maximum coronary artery z-scores at baseline and at 6–8 weeks follow-up.

This study must be viewed in light of some potential limitations inherent to its retrospective design. Nevertheless, the amount of missing data are limited, and the very large sample size relative to previous studies ensures that a large enough number of patients have sufficient data to allow inferences to be drawn from this cohort. Measurements of blood pH are not routinely performed as part of the laboratory work-up for KD. Therefore, we can only speculate that Gamimune[®] causes blood acidification which, in turn, might lead to worse coronary artery outcomes. Finally, a detailed review of adverse effects associated with IVIG treatment was not available in this cohort. A recent comparison of the adverse effects associated with these specific IVIG preparations in the context of juvenile dermatomyositis found that Gamimune[®] was associated with a higher frequency of non-life-threatening adverse effects than Iveegam[®], and this difference was attributed to Immunoglobulin A content (9).

In conclusion, our study suggests that, after controlling for potential confounding, the use of Gamimune[®] for the treatment of KD is associated with faster defervescence and lower probability of non-response to IVIG, but more importantly, higher coronary artery z-scores at the end of the acute phase and 6–8 weeks later. Higher Gamimune[®] concentration might explain why Gamimune[®] had a faster effect in terms of fever reduction. Stabilization through acidifica-

tion as used for Gamimune® rather than with glucose as used for Iveegam® led us to speculate that worse coronary artery outcomes might be associated with physiologic changes caused by blood acidification in the context of weakened vascular walls as a result of KD. Our study suggests that, when the option is available, IVIG preparations that are not stabilized through acidification might be preferentially used for treating patients with KD. Future research might focus on exploring the link between blood acidity and coronary artery outcomes in KD.

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