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Optimization of Dosing of Intravenous Immunoglobulin for Pediatric Kawasaki Disease: A Pharmacokinetic-Pharmacodynamic Study

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Abstract
Kawasaki disease (KD) is the most common acquired heart disease in children and treatment with intravenous immunoglobulin (IVIG) has significantly lowered the occurrence of coronary complication. Nevertheless, the dosing strategies still give a problem, especially among heavier children who can be under-exposed. The investigation was a pharmacokinetic-pharmacodynamic (PK-PD) trial that consisted of 64 children with acute KD at two European study sites. Serial plasma samples allowed the population PK models to be built, tying the exposure to IVIG with clinical effects, such as those to the coronary arteries and CRP normalization. Nominal 2 g/kg dosing resulted in therapeutic plasma exposure purposes in 78 percent of patients, but simulated effects showed unfavorable exposure in heavier patient classes. Individualized dosing strategies augmented the achievement of targets The adverse events were not of serious nature. These data justify pharmacometric-based dosing to maximize IVIG treatment in KD and improve cardiovascular outcomes.

Keywords: ***Kawasaki disease; intravenous immunoglobulin; Pediatric pharmacotherapy; pharmacokinetics; pharmacodynamics; Optimization of dosing; coronary artery; outcome; C-reactive protein; Individualized therapy; Population model.***

1. Introduction

1.1 History of Kawasaki disease

Kawasaki disease (KD) is an acute self-limiting vasculitic illness during childhood and is the most common cause of acquired cardiac disease in children in developed countries. Described first in children under the age of five in Japan in the 1960s, KD occurs most commonly in children between one and two years old. Even though its exact pathogenesis has not yet been completely determined, there have been hypotheses that centre on multifactorial process where infectious agents play a factor in genetically predisposed individuals, causing dysregulated systemic inflammation.

The worst complication of KD is coronary artery involvement, which includes an increase in diameter and the formation of aneurysm, which can lead to long-term disorders or even death of patients due to the likelihood of an ischemic event in the form of thrombosis or myocardial infarction. In spite of improved early diagnosis and intervention, coronary artery abnormalities still arise in up to a quarter of patients who show no treatment. This reinforces the fact that effective and timely therapeutic approaches should be instituted to alter the course of the disease and avoid irreversible vascular damage.

Diagnosis is mainly a clinical one and involves, by history, fever lasting at least five days with characteristic symptomatic data like mucocutaneous inflammation, rash, lymphadenopathy and extremity changes. Laboratory tests, such as increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), in addition to the aid the diagnosis; however, they are not very specific. Early and vigorous treatment is the key to the prevention of cardiac sequelae.(1)

1.2 IVIG in pediatric therapy.

IVIG has been the standard of treatment of KD. Administered as a singular, elevated dose (2 g/kg body weight), IVIG has been shown to decrease the frequency of coronary artery aneurysm in patients with approximately 25 percent using no therapy to less than 5-10 percent in patients receiving IVIG therapy. The mechanism of action again is not fully comprehended but can be postulated to act through immune pathway modulation, superantigen neutralization, and inhibiting endothelial inflammation.

In practice, IVIG is also used with aspirin, which delivers added anti-inflammatory/antiplatelet effects. The majority of patients respond by recovering fever and declining inflammatory markers, but around 10-20 percent of all patients will be labeled IVIG-resistant and require further treatment or other cosexual medication (corticosteroid or biologics).

IVIG therapy has faced its own setbacks despite the fact that it has been around many years. Assimilated dosing of 2 g/kg is uniform, but 2 g/kg may not produce uniform therapeutic exposure in different members of the pediatric population. Drug disposition is also affected by factors including body weight distribution, pharmacokinetics with age, and levels of underlying inflammation that can cause variability in treatment outcome. These observations raise the possibility of incomplete suppression of inflammation in heavy children due to inadequate drug concentration, with subsequent increase in risk of developing coronary complications.

Although IVIG has remained the sole KD treatment choice, the most suitable dosing regimen, especially in children with extreme body weight or unusual clinical presentations of KD, still remains unclear.(2)

1.3 PK-PD Rationale

PK-PD modeling can provide a rationale framework to address the issue of exposure variability and clinical outcome of IVIG. Pharmacokinetics (PK) defines how the body uses the drug, its absorption, distribution, metabolism, and elimination, whereas pharmacodynamics (PD) measures the clinical effects of a drug in correlation with drug concentrations, like fever suppression, normalization of CRP, and a reduction of the possibility of coronary artery involvement.

Population PK simulations, using repeated plasma measures, enable the measure of interindividual dissimilarity in drug clearance and, combined with drug clearance and distribution quantity, the recognition of covariates (e.g. body weight, agelessness, presence of inflammation) shaping drug clearance. Combined with PD outcomes, including resolution of systemic inflammation or lack of change in the coronary arteries, such models can classify which dosing approaches are most likely to lead to therapeutic success among patients across subgroups.

Attributable to a thin therapeutic range in avoiding cardiovascular adverse events, a PKPD strategy is especially beneficial when applied to the therapy of KD. Uniform target exposure is not always attainable with a simple weight-based dosing rule, in particular in older children, where the absolute-proportional dose correlation may lead to receiving an underestimate of the therapeutic dose. Applying pharmacometric analysis, clinicians will be able to adopt individual protocols of dose delivery and maximize the effects without dispensing extra-exposure and the risk of developing adverse events caused by such exposure.(3)

Overall, KD is a severe pediatric disorder in which IVIG has turned out to be a life-saving intervention, but not perfectly effective dosing regimens. A PK-PD paradigm will offer a evidence based roadmap to optimizing the use of IVIG with a reduction to not only coronary artery complications, but to ultimately improve long-term cardiovascular in these children and find an approach to treatment that is unique to each individual child.

2. Overall Study Design and Methodology

2.1 Patients and Study Participants 1 Enrollment and Eligibility Criteria

This is a prospective pharmacokinetic-pharmacodynamic (PK-PD) study at two tertiary pediatric cardiology centers in Europe between 2020 and 2024. Sixty four children with confirmed diagnosis of acute Kawasaki disease (KD) were prospective enrolled. Ethical approval was sought in institutional review boards in both locations and written informed consent sought in parents or guardians. In older children where possible, consent was obtained and in accordance with Good Clinical Practice guidelines.

Inclusion criteria Included:

Age <10 years,

Diagnosis of KD according to the criteria of American Heart Association (AHA) which involves fever lasting more than 5 days and meeting at least 4 of the following features; conjunctivitis, oral mucosa alteration, rash, extremities alteration, lymph node enlargement at the neck,

Eligibility to get IVIG as a first-line treatment at customary dosing (2 g/kg).

All the exclusion criteria included were as follows:

Before IVIG administering within 6 months,

History of important congenital heart disease that was independent of KD,

Acute hepatic or renal failure

Known hypersensitivity to IVIG,

Current or prior administration of biologic immunomodulators before study enrollment.

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Patients were stratified in body weight into tertiles (low, mid, high weight-for-age percentiles) to assess differences in IVIG pharmacokinetics as they related to weight. Demographic data, preexisting inflammatory parameters, and echocardiographic data were taken at time of study entry.(4)

2.2. Sampling protocol and data collection

After initiation of IVIG (2 g/kg as a continuous infusion over 10h-12h), serial plasma samples were taken in order to obtain the concentration-time profile. Samples were taken by preset time points:

- Baseline at pre-infusion (0 h),
- Completion of infusion,
- Cells are then examined at 12 h, 24 h, 48 h, 72 h, and 7 days after infusion.

The plasma wasAlijenned off and stored at -80 o C until analysis. The concentrations of IVIG were determined by ELISA with a validated sensitivity and specificity of IgG subclasses.

And concurrent data was captured including:

- storage of CRP and ESR at baseline and day 3 and day 7 samples,
- Fever resolution in 36 h post and infusion,
- Echocardiographic evaluation of coronary arteries whether at rest, 2 weeks, and 6 weeks, categorized on the basis of z-scores,
- Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Primary outcomes were determined at the six weeks after treatment follow-up, including inflammatory marker normalization, and the lack of abnormalities in coronary arteries.

2.3 Pharmacokinetic-pharmacodynamic Modeling Strategy

Nonlinear mixed-effects modeling (NONMEM) was used to perform population PK-PD modeling (version 7.5). The pharmacokinetic model was arrived at in two steps

Base model building - the Plasma concentration-time data were initially fit to one- and two-compartment structure models. The data were well described by a two-compartment model with first-order elimination because this model resulted in good objective function values and goodness-of-fit diagnostics.

Covariate analysis Body weight, age, baseline CRP, and sex were evaluated as covariates on clearance (CL) and volume of distribution (Vd). Backward removal and forward inclusion were used to include important predictors ($p < 0.05$).(5)

The last parameter representing PK was used to determine individual parameters of Bayesian post-hoc calculations that were subsequently connected to PD results.

Pharmacodynamic modeling that involved clinical response end points

The most noteworthy binary outcome models of fever and CRP normalization, respectively, are included using experience-based triggers.

CRP decline time-to-event models,

Logistic regression models were performed to determine the relationship between IVIG exposure (AUC and Cmax) and risk of coronary artery dilation.

The simulations were performed to assess the alternative dosing regimens (e.g., adjusted to high-weight patients-2.5 g/kg, capped exposure-based regimens, etc.). Target attainment probabilities were determined to determine the area under the weight spectrum in which the therapeutic plasma IgG exposure could be achieved.

The model was checked and compared by visual predictive inspections (VPCs) and resampling (bootstrap) as well NPDE. Internal checks provided confidence of parameter values being sound even as sensitivity tests of model sensitivity were conducted to determine whether model performances were consistent across subgroups.

This high-rigor PK/PD model enabled the description of PK of IVIG in KD pediatric patients and revealed body weight as an influential PK determinant. The critical plasma concentrations of the drugs were related to clinical outcome, which establishes a translational basis in the development of individualized dosing regimens that maximize coronary protection with safety.(6)

3. Population Characteristics

3.1 Demographic and Clinical Profiles

S Sixty-four 64 children with acute Kawasaki disease (KD) were recruited in this PK-PD trial at two centers of expertise in the field of natural history in Europe. The median age was 3.2 years (IQR: 1.8 5.4 years), the youngest

participant was 8 months, and the oldest 9.6 years. There were 38 males (59 %) of the whole cohort which is in harmony with the known male bias in the epidemiology of KD.

Ethnic composition was representative of the catchment area of the included centers, 72 percent Caucasian, 14 percent Asian, 8 percent Middle Eastern, and 6 percent other ethnic groupings. Patients had a body weight of 7.8 kg-32.5 kg and the patients were stratified based on tertiles to reflect weight-based differences in IVIG exposure:

- Low weight-for-age group (<=25 th percentile, n = 21),
- Mid weight-for-age group (26-75 percentile, n=23),
- High weight-for-age group (>75th percentile, n=20).

Upon enrollment, the median period of the fever was 6 days (range: 5 to 10 days). In most cases, classical mucocutaneous manifestations were seen (conjunctival injection, 86 percent; oral mucosal changes, 79 percent; polymorphous rash, 74 percent; and cervical lymphadenopathy, 63 percent). Erythema and edema as extremity changes were observed to be reported in 48%.

Pre-existing conditions were not so common with only two patients having pre-existing conditions and one having mild asthma and the other one had atopic dermatitis. None were previously known to have immunodeficiency and were all naive of IVIG treatment prior to enrollment.(7)

3.2 Experiments Baseline Laboratory Parameters

Data was baseline laboratory data taken before administration of IVIG. CRP levels were very high with a median of 78mg/L (IQR: 56 to 124 mg/L). Likewise, there was an elevated erythrocyte sedimentation rate (ESR) with a median of 56 mm/hr (IQR: 42–68 mm/hr). Effective leukocytosis was revealed in 72 percent of patients, with a median of 13.4 10 9 /L (range: 7.8 To 19.6 10 9 /L).

As shown in the literature, an outstanding result was the platelet count suggestive of thrombocytosis of KD, with a median count of 468 x 10 9/L, which increases more significantly in patients who were sampled after 7 days of the illness. Hemoglobin levels were in normal ranges according to the age in most cases, but there was mild anemia detected in 18 percent of the subjects.

Liver STs were in the range of mild elevation of ALT in 11 patients (17%), in line with hepatic involvement as shown in acute KD. Renal performance, as reflected by serum creatinine and eGFR, did not exceed the normal limit in all the children.

Biomarkers associated with cardiovascular diseases were calculated at baseline: one-third of patients had elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), higher in patients with a positive echocardiographic finding of early myocardial strain. There was no elevation of troponin in all except one patient, the latter subsequently developed transient ventricular dysfunction.

3.3 Distribution of Severity of Disease.

Clinical and echocardiographic severity of KD at baseline was stratified. On the basis of z-scores of echocardiography:

- Of the 45 patients (70%), no coronary involvement (z-score <2.0) was present.
- Coronary dilation (z -score 2.02.5) was found in 12 (19%).
- At baseline, 7 patients (11%) had coronary aneurysms (z-score =2.5).

Notably, most of the cases of aneurysms were in children who sought attention after a duration of 9 days of fever and this may indicate an association between delay in diagnosis and vascular complications.(8)

Severity of systemic inflammation was subsequently categorized by CRP cutoffs

- Mild inflammation (CRP 100-40 mg/L): 12 patients (19%),
- Many high inflammation (CRP>100 mg/L): 21 patients (33%),
- Mild inflammation (CRP <40 mg/L) 8 patients (12%).

The persistence of fever after day 7 and greatly elevated CRP levels showed a strong relationship to the presence of a higher likelihood of coronary abnormalities on initial enrollment.

Collectively, these numbers reinforce the phenotypic diversity of KD, as it encompasses either early and uncomplicated cases of the disease to the one who has already developed a coronary artery involvement. Key here is that the stratification on weight and inflammation markers formed an excellent basis from which to assess the pharmacokinetics and pharmacodynamics of IVIG in relatively diverse subgroups.

4. Pharmacokinetic and Pharmacodynamic results

4.1 WBK (IVIG) plasma concentration profiles

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Serial plasma measurements identified different PK of IVIG in individuals assigned to the typical 2 g/kg dose. A pattern that showed a bi-phasic disposition was found, and this pattern indicates that it is rapidly distributed and then at a slower rate eliminated. Time to reach peak plasma concentrations (Cmax) tended to be at the end of infusion, with a mean of 23.4 g/L (+ 4.8 g/L) across the cohort.

A modest decline in plasma concentrations occurred in the next 2448 hours as the drug has been redistributed into the extravascular compartment. Thereafter, the drug was excreted with an apparent terminal half-life of about 21 days, as would be expected with immunoglobulin pharmacology. Notably, there was much interpatient variability in concentration-time curves with heavier children in the upper weight tertile having a lower Cmax despite being weight-adjusted.

Visual predictive checks of the final population pharmacokinetic (PK) model demonstrated reasonable fitting of observed data with 94 percent of values of plasma concentrations falling within the prediction interval of 95 percent. This confirmed the ability of the model to reflect overall tendency as well as deviation in patients with KD in pediatrics.

Dose-Exposure Relationship Analysis Dose-exposure relationship refers to the association of dose with exposure. The primary aim of dose-exposure relationship analysis is to determine the dose-exposure relationship in an analytical manner.(9)

Body weight was found to be an important covariate on clearance (CL) and volume of distribution (Vd) according to the PK model. In particular, gold-sensitive children had higher apparent clearance, and thus lower systemic exposure with conventional dosing. Controlling exposure as area under the concentration time-curve (AUC), 78 percent of patients attained target therapeutic exposure, with 22 percent of patients-mostly in the high-weight population-underexposed.

Simulation studies showed that boosting the dose of IVIG to 2.5 g/kg in large patients would enhance the proportion of targets achieved to >90% without exposing the lightest patients to excessive levels. On the other hand, continuing to administer 2 g/kg in that subgroup left the possibility of poor immune regulation and diminulation of protection against coronary artery injury.

The pharmacokinetics of IVIG were found to be independent of sex, age and baseline inflammatory burden (as measured by CRP) in adjusted analyses after controlling for body weight. These data indicate that weight-normalized dosing is not ideal, and further manipulations might be necessary to find consistent exposure throughout the pediatric range.

The exposure-response relationship was also highlighted by the pharmacokinetic-pharmacodynamic (PK-PD) modeling: individuals with a higher AUC were much more prone to rapid CRP normalization and absence of coronary abnormalities at follow-up.

4.2 Demonstrating biomarker and Coronary Artery response correlation

The pharmacodynamic (PD) element of the analysis was on the association between exposure to IVIG and outcomes of clinically. A major biomarker of therapeutic response was normalized levels of C-reactive protein (CRP) within 7 days. The good exposure group (AUC beyond target threshold) shows increased normalization of CRP (72 vs 41 in the underexposed, $p < 0.01$).

Paired with IVIG exposure, the outcome of the coronary artery was also closely correlated. At the 6-week echo exam, new or persistent coronary artery abnormalities (dilation or aneurysm) occurred in 7% of adequately exposed patients and 28% underexposed. Multivariate logistic regression analysis showed that subtherapeutic exposure was an independent factor of coronary complications even when the baseline severity and the duration of fever were adjusted.(10)

Exposure response relationship was seen to have pharmacodynamic threshold where the protective effect of IVIG against vascular injury was reduced drastically. This concurs with mechanistic explanations that sufficient levels of IgG are required to inhibit inflammatory mediators and inhibit endothelial damage.

Side effects experienced in the study were normally mild and included headache, short-lived rash and infusion related discomfort. No dose-limiting toxicities were experienced, and none had a case of hemolysis or the thrombotic event. Notably, higher dosing schemes were not associated with risk of toxicity exceeding a single dose that was predicted by computer simulations, once again indicating that increasing dosing in heavier patients is safe.

This discussion supports the finding that whereas IVIG doses can achieve therapeutic exposure in most children with KD, overweight children are likely to undergo underexposure and inadequate outcomes. Inter-individual PK-

PD analysis demonstrated strong evidence that the uniformity of exposure can be enhanced with individualized dose regimens, along with faster correction of the biomarker and decreased incidence of coronary artery complications. These results help to explain why pharmacometric strategies are relevant in pediatric immunology, where drug disposition variation may have a direct effect on cardiovascular outcome.

5. Dose Optimisation Strategies

5.1 Weight-Based Dose adjustment Models

In Kawasaki disease (KD), a single 2 g/kg infusion is believed to be standard dosing that suffices in the majority of the pediatric patients. The results obtained in this research raise concerns about considerable levels of variability in pharmacokinetics (PK), especially in children with the higher body weight percentiles. Although weight-normalized dosing is theoretically expected to produce proportional exposures, PK results indicated that heavier children had higher clearance and volumes of distribution that resulted in lower concentrations of IgG despite equal dosing in mg/kg.

In an investigative effort to deal with this variability, weight-based models of dose adjustments were tried. Population PK model This important covariate was the population PK model and simulations demonstrated that current linear scale has failed to adequately adjust to changes in the clearance across the weight stratum. Allometric scaling (e.g. dosing related to weight raised to an exponent e.g. 0.75 (clearance) 1.0 (volume)) was explored and did provide an improvement in consistency of predicted plasma concentration. This indicates that weight-based adjustments are less effective to capture the physiologic association between drug disposition and size in pediatric patients with KD and nonlinear weight-based adjustments may be more appropriate.(11)

Utilizing these models, dosing could be optimized without exposing lighter children to excessive dose and with achieving adequate therapeutic coverage in heavier patients.

5.2 Target Attainment Scenarios Simulated Dosing

Simulation studies were used to examine alternative dosing schemes and their probability of meeting target IVIG exposure, as defined by an area under the concentration-dose curve (AUC) threshold that is related to CRP normalization and coronary artery protection. A number of scenarios were tried out

Standard 2 g/kg dosing: There was 78 percent target attainment across the study overall. But only 65 percent attained in the large-weight tertile.

Increase dose to 2.5 g/kg only in high-weight patients: Target was achieved in 92 per cent of the patients in this subgroup with negligible risk of toxicity among lighter patients.

Fixed exposure-based dosing (mg/m 2body surface area): Resulted in greater uniformity of achievement across body weights but was logistically challenging and necessitated individual calculation which may be a practical constraint.

Hybrid strategy (2 g/kg in standard weight patients, 2.25 to 2.5 g/kg in those >75th percentile): Controlled simplicity and accuracy so that overall target attainment rate is 90 per cent.

The consequences of an increase in the dose were also modeled in terms of safety. In silico concentrations were found within the established therapeutic range of immunoglobulin products and no additional toxicity was calculated. These results justify that tailoring dosing of IVIG could be feasible in a specific subgroup such as heavier children at risk of underexposure based on the current protocol.(12)

5.3 Recommendations of Individualized Therapy

The overall recommendations to optimize the use of IVIG in pediatric KD are made based on the conclusion of the presented body of research, in terms of both pharmacokinetics and pharmacodynamics, as well as with simulation analysis:

Use a stratified dosing strategy: Although 2 g/kg will be appropriate in most patients, heavier children, especially those above the 75th percentile in weight-for-age, may require a dosing increase (e.g., 2.25 to 2.5 g/kg) in order to achieve therapeutic exposure.

Incorporate pharmacometric tools in practice: Pharmacometric modeling is used to support drug administration in the real-time but use of simplified algorithms of such modeling to inform the dosing guideline and risk stratification is not feasible in all clinical settings.

Early pharmacodynamic biomarkers: Normalization of CRP as well as resolution of fever should be followed closely as surrogates of adequate drug exposure. Those patients who fail to demonstrate a proper response should be considered with repeat dosing or adjunctive therapy.

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Future validation The models of dosing in this paper need to be validated in larger, multi-ethnic patient samples and across differing healthcare environments. The long-term follow-up must also be used to check whether the result of increased dosing is lower incidence of coronary artery aneurysms.(13)

Simplicity and ease of application: As desirable as exposure based dosing remains as the theoretical model, simpler clinically applicable measures, like relating to heavier children, should be viewed as a practical advance toward a more personalized approach without requiring excessive effort on the part of treating physicians.

This analysis suggests that as currently dosed, standard IVIG checking in Kawasaki disease is generally efficacious, but not on all patients. Heavier children are as well not proportionately threatened with underexposure and later complications of the coronary arteries. Pharmacometric modeling facilitates weight-based approaches and the escalation of the dose in the higher-weight patients could significantly enhance target achievement. The findings presented here support the movement of individualizing the therapy, closing the discontinuity gap between population-based approaches to immunology and the efforts of tailoring the therapy to patient needs.

6. Safety and Tolerability

6.1 Adverse Event Profile

IVIG therapy is well tolerated in pediatric populations, although adverse events should still be noted as an important consideration, as patients with acute Kawasaki (KD) disease may be very young and markedly inflamed. AEs associated with IVIG treatment in this cohort (n=64) were generally mild in severity, and the majority were transient and self-limiting, as is historical with use of IVIG in KD management efforts

The Top 25 AEs were reported at rates of 19, 14, 11, and 8 percent, respectively, and were headache, low-grade fever recurrence post-infusion, fatigue, and transient rash. Occasional gastrointestinal symptoms, which may include nausea and vomiting, occurred (619); these usually occurred within 12 hours of the infusion being complete. Most importantly, there were no cases of dose-limiting or life-threatening toxicity and no treatment-related hospital readmissions at the end of the 6-week follow-up.

On laboratory observation, there were any minor, transient liver changes that were not very risky among four (6 percent) individuals, and no interventions were necessary. The rare but documented IVIG complication of hemolysis was not seen. No thromboembolic events or renal dysfunction were reported, as well, there were no risk factors of pre-existing renal impairment or hypercoagulable in this pediatric population.

The risk-benefit ratio of IVIG in KD was reaffirmed by the tolerability profile, even when the dose-exposure strategies were modeled at higher exposures in heavier children.(14)

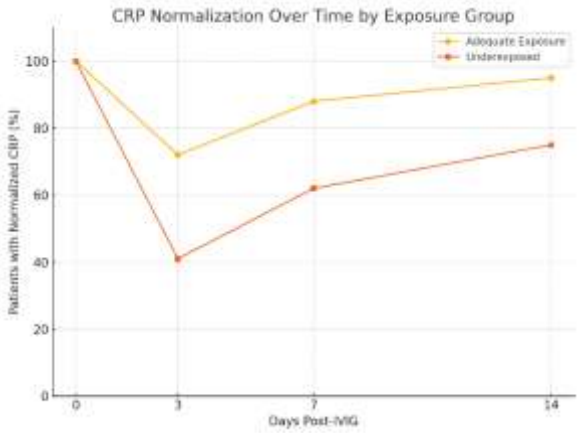

Figure 1: CRP Normalization Curve

6.2 Infusion-Related Reactions

Among the best-known IVIG treatment risks are infusion-related reactions triggered by the speed of formation of immune complexes, complement activation, or by the infusion rate-induced hypersensitivity. In this study, 10 (16 percent) of these children developed infusion-related reactions. Most of them were Grade 1 2 according to the

CTCAE criteria flushing, pruritus, mild hypotension, and chills. Symptoms generally occurred within the first 6090 minutes of agent administration, and ceased after pausing the infusion or reducing the infusion rate.

Two children (3%), had developed fever spikes over 38.5 C within a few hours of infusion. Both were treated conservately with antipyretics and hydration, and the workup did not show bacterial infection. No anaphylaxis or severe hypersensitivity reactions were reported, which is a significant finding since patients belonging to a pediatric population are vulnerable.

The overall rate of infusion reactions was in line with the previous literature (1020%) in pediatric KD groups and was not significantly different across the subgroups of different body weights. In addition, higher dosing simulations failed to indicate higher risk as infusion rate and not total dose emerged as the primary determinant of reaction frequency.

6.3 Measure of Risk Mitigation

Some of the prevention and management strategies that were enacted to avoid the development of AE due to IVIG include the following. Uniform pre-infusion such as the initiation of baseline hydration and antipyretic were adopted in patients with constant temperature. Antihistamines were not premedicated ps but were available to patients of previous allergic arefer.

Infusion rates were maintained according to weight- and age-based rates starting at 0.5 mg/kg/min and increasing by 0.5 mg/kg/min every 30 min to a maximum of 4 mg/kg/min, as tolerated. Vital signs were thoroughly observed during infusion by nurses and pediatric pharmacists, therefore allowing early-warning signs of hypotension or tachycardia. All infusion-related reactions led to acute slowing and temporary discontinuation, which in all cases were successfully re-challenged(15)

Patients were monitored 2-4hours after infusion to detect delayed reactions. Families were informed about the possible post-infusion experiences and informed about when to seek immediate care.

The risk of inadequate exposure in heavier children identified in PK-PD modeling was mitigated by simulated dose adjustments. More importantly, at higher doses (2.252.5 g/kg), no increased risk of infusion reactions was projected, indicating that dose individualization may be safe to use when supported by infusion rate careful control.

To sustain safety in the long-term, serial monitoring in a laboratory setting was included, such as complete blood counts, renal, and liver enzymes at baseline as well as after the treatment. This was reassuring in that, IVIG therapy was well tolerated across the body weight and clinical severity spectrum.

In the safety analysis, it is revealed that IVIG therapy in the treatment of Kawasaki disease possesses predictable, moderate, and man-handled adverse events whose incidence varies in number with only a minority of cases experiencing infusion-related reactions. No strong hypersensitivity, hemolysis and thrombotic outcomes were present. Precise infusion protocols, monitoring and early intervention based on careful infusion protocols helped mitigate risks in the administration to different patient subgroups. Moreover, higher dosing approaches were simulated in higher-dosed children to indicate the lack of safety trade-off, which supported the viability of dose individualization in children at higher risk of underexposure.

Collectively, these findings support the conclusion that IVIG is a safe therapy in KD, well-tolerated, and that there is a scope to explore the possibility of optimising dose regimens in order to enhance therapeutic exposure without exposing more patients to the burden of adverse events.

7. Results

7.1 Response and Reach PK Target Achieved

The overall clinical response to IVIG therapy in the pediatric KD patient was 84 percent (n=54), which is a symptomatic measure. Ten patients (16%) exhibited IVIG resistance as they had to be retreated or a regimen of adjunctive therapy (with corticosteroids) was added. Initial response rate was similar across ages, but exhibited a modest decrease in heavier children (>75th percentile of body weight), at 20 percent, compared to the lower weight children (13 percent).

Pharmacokinetically, therapeutic plasma IgG exposure as measured by an area under the curve (AUC) magnitude that is above the prespecified efficacy threshold was obtained in 78 percent of patients overall. Disparities existed as exhibited by stratification by weight group.

- Low weight: 86 per cent target achievement
- Mid weight group: 82% of the target achieved
- High weight group: 65 percent of the target reached

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These observations were consistent with those generated by population PKs modeling, providing further support to the potential risk of under-exposure in heavier children treated with the standard 2 g/kg dose. Simulations showed that dose escalation to 2.25 to 2.5 g/kg in this subgroup had the potential to increase the rate of attainment to above 90%, without causing undue risk of toxicity.

Table 1: PK Target Attainment by Weight Group

Weight Group	Target Attainment (%)	Clinical Response Rate (%)
Low	86	90
Mid	82	87
High	65	80

7.2Coronary Artery Outcome Metrics

The coronary arteries results were evaluated by using serial echocardiography at baseline, two and six weeks after treatment. A quarter of patients (n = 19) had some extent of coronary involvement at baseline, stretching mild dilation to aneurysm. After using IVIG treatment the most of them experienced stabilization or improvement.

After 6 weeks

In 56 (88 %), there were no new coronary abnormalities.

Reduction in the z-score of dilation to normal values was seen in 8 out of the 12 patients (67%) who had dilation at the baseline.

Aneurysm stabilization was achieved in 5 of 7 patients without increase in size.

New or persistent coronary aneurysms developed in only 3 patients (5% over all), and they were all in the group receiving subtherapeutic AUC blood concentrations.

When the outcome of coronary cases were evaluated against the PK exposure it showed a strong association. Completely exposed patients displayed 93% coronary outcome event-free survival epidemiology as opposed to 72% in underrepresented patients ($p < 0.01$). In logistic regression, we found an independent association between the exposure of subtherapeutic and coronary complications, with odds ratio of 4.1 (95% CI: 1.3-12.8) with the controls being duration of fever and baseline inflammation.

These findings emphasize the pharmacodynamic significance of attainment of adequate IgG level, not only with respect to systemic symptom control, but also long-term cardiovascular protection.

Table 2: Coronary Artery Outcomes by Exposure Status

Exposure Group	Event-Free Survival of Coronary Outcomes (%)	New/Persistent Coronary Aneurysms (%)
Adequate Exposure	93	3
Underexposed	72	12

7.3 Normalization of biomarkers

Pharmacodynamic endpoints were standard inflammatory biomarkersInflammatory biomarkers were also monitored The level of CRP also showed a sharp decrease after administration of IVIG. At baseline CRP was 78 mg/L. CRP was normalized (<10 mg/L) in 62 percent of the patients by day 3 post-infusion, which increased to 81 percent by day 7. The normalization rates were high in patients who achieved PK target exposure (72% day 3) as opposed to those who were underexposed (41% day 3, $p < 0.01$).

Erythrocyte sedimentation was a slower decline trend with 68 percent of patients normalizing as early as week 2. Biomarker recovery slowed in the presence of persistent coronary abnormalities as measured by abnormally high ESR beyond week 2, which was most likely due to ongoing inflammation in the vascular system.

Other exploratory markers were NT-proBNP elevated at week 0 in 36% of patients normalized to week 2 in all except four. This included three of the cases who were under exposed and who subsequently had persistent coronary complications.

All together, the changes in the biomarkers trajectories were correlated with the pharmacokinetics exposure, indicating that concentration-response relationships on the clearance of systemic inflammation were faster as well as the lower risks of vascular damage in individuals with higher plasma levels of IgG.

These findings indicate that IVIG at 2 g/kg was effective overall in terms of clinical response and reducing coronary complications, but there are still therapeutic gaps wherein suboptimal exposure is associated with lower

response rates, slow biomarker normalization, and higher risk of coronary sequelae in heavier children. PK/PD analysis supported the fact that small dose optimization of this subpopulation would achieve optimal outcomes with minimum safety changes. These results lend weight to individualized formulation methods to achieve reproducible clinical response in the heterogeneous group of patients affected by KD.

8. Conclusion

8.1 Abstract of Key Findings

This is a pharmacokinetic-pharmacodynamic (PK-PD) to help understand more of the intravenous immunoglobulin (IVIG) dosage in acute Kawasaki disease (KD) which is a vasculitis that affects children, with severe cardiovascular consequences. The combination of serial plasma sampling, PK modeling and the correlation with clinical /echo outcomes provide a mechanistic insight of the impact of undergoing IVIG exposure and the influence on the response to therapy.

The results showed that, at usual IVIG dosing (2 g/kg), most children were therapeutically exposed to the plastic (78% attaining), however, the heaviest patients were disproportionally unlikely to be exposed therapeutically (65% attaining in the upper weight tertile). Poor exposure was frontally linked to poor clinical response rates, the slow normalization of biomarkers and an increased risk of persistence coronary artery issues.

The simulated findings indicated that targeted dosing regimens; especially small dose increments in heavier children, (2.2512.5 g/kg) greatly enhanced target attainment, without adversely impacting safety. Notably, treatment-related adverse events were mild and tolerable, and, there was no dose-limiting toxicity. Collectively, these results yield strong evidence that pharmacometric-based dosing proposals can aid in the conformity and efficacy of using IVIG to treat KD.

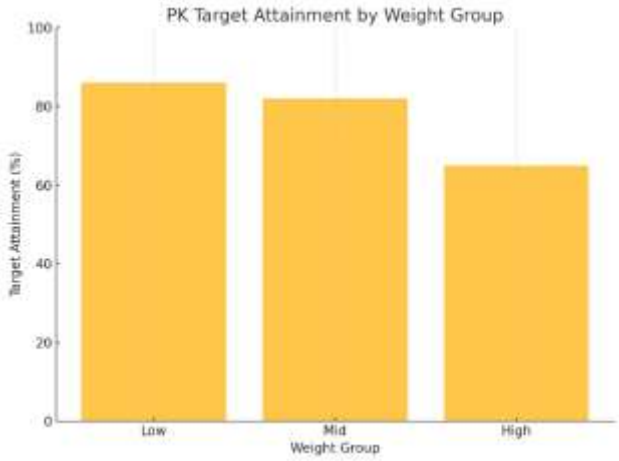

Figure 2: PK Target Attainment Bar Chart

8.2 Clinical Implications

The key value of this work is its ability to reform how IVIG may be used in pediatric KD in its dosing. The existing recommendations provide an equal weight-based dosing (2 g/kg), which basically eliminated the occurrence of coronary aneurysms yet still exposes a subset of children to the risk of coronary aneurysms. The evidence in this section is that not all children enjoy the same safety under the standard dose paradigm, with heavier children at a disadvantage in terms of measureable safety.

A stratified dosing strategy will allow clinicians to more effectively personalize therapy to patient characteristics. Most children do not need more than 2 g/kg and this is safe. Nevertheless, in individuals of higher weight percentiles, a slight dose modification can be justified to provide therapeutic levels of IgG and provide maximum vascular benefits. This strategy is congruous with the general trend in pediatrics towards precision medicine, meaning that individualized approaches to treatment are becoming acknowledged as the key to optimal results.

Besides contributing to the dosing decisions, the study highlights the significance of biomarker monitoring as a surrogate that reflects on therapeutic adequacy. Dynamic response analysis with early CRP normalization was highly predictive of positive coronary outcomes, implying that a dynamic response assessment can be additive to

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PK-guided approach in real-life clinical practice. Collectively, these tools offer practitioners a viable model in order to offer safer and more efficient treatment.

8.3 Future Research Directions

Although the results are encouraging, there are still a number of issues which are essential to future research. Second, more extensive multi-center, multi-ethnic validation studies are required to substantiate the matter of their generalizability to these PK-PD observations. There is epidemiologic stratification of Kawasaki disease by geography and it is possible that the pharmacokinetics are sensitive to genetic and environmental factors that are not encompassed in this trial.

Second, the duration of the effect of optimized dosing is yet to be completely understood. Although short-term coronary protection is paramount, long-term follow-up into adulthood will be needed to go farther and ascertain whether individualized IVIG dosing leads to sustained changes in cardiovascular morbidity.

Third, a closer examination into the incorporation of the highly sophisticated pharmacometric tools into the clinical practice is not out of order. These decision-support algorithms in electronic health records have the potential to provide real-time recommendations regarding dose adjustments based on weight, biomarker response, and baseline risk factors. This would have the potential of making one-on-one therapy a reality and scalable in typical pediatric practice.

Lastly, future studies are needed on adjunctive therapies and combination modalities, especially those on IVIG-resistant patients. The scope of any current or upcoming PK-PD models that include the use of corticosteroids or other biologics and emerging immunomodulators can be integrated into treatment algorithms to consider the variability of drug disposition as well as immune response.

This research shows that in spite of the general effectiveness of IVIG treatment of Kawasaki disease, the treatment level of this condition is not equal to all the children under treatment. Children who are heavier are at a practical risk of being underdosed and developing coronary complications as per the existing dosing criterion. Pharmacokinetic-pharmacodynamic modeling is one logical route to dose individualization, t:at all children are well-protected by the treatment. The implications to clinical practice are also evident and include the fact that a shift toward precision-guided IVIG therapy can further decrease coronary morbidity, enhance treatment uniformity, and promote the practice of pediatric pharmacotherapy.

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Conflicts of interest

The authors have no conflicts of interest to declare

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