Safety and Pharmacokinetic Evaluation of Intravenous Vaccinia Immune Globulin in Healthy Volunteers

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(See the editorial commentary by Bray on pages 767–9 and the review by Hopkins and Lane on pages 819–26)

Background. Vaccinia immune globulin (VIG) administered via the intramuscular route has historically been used for the treatment of complications of smallpox vaccination. Intravenous formulations of VIG are required to improve tolerability and pharmacokinetic profile.

Methods. We conducted 2 separate studies to evaluate the feasibility of administration of an intravenous formulation of antivaccinia immune globulin (VIGIV). The first study assessed the pharmacokinetics and safety of a newly manufactured lyophilized VIG product for intravenous administration (VIGIV-lyo). Seventy-eight healthy volunteers received an intravenous infusion of VIGIV-lyo at doses of 100 mg/kg, 200 mg/kg, or 500 mg/kg. In the second study, we evaluated the safety of a liquid product of VIGIV (VIGIV-liq) in 33 healthy volunteers receiving an intravenous infusion of 100 mg/kg VIGIV-liq.

Results. The geometric mean titer of VIG at the target dose (100 mg/kg) after intravenous administration is 2.5 times higher than the predicted geometric mean titer after intramuscular injection (P<.001). The pharmacokinetics of VIGIV-lyo are linear for doses from 100 mg/kg through 500 mg/kg. Administration of the 200-mg/kg and 500-mg/kg doses of VIGIV-lyo does not result in markedly higher adverse event rates. The adverse event rates observed with the liquid product are comparable to those seen with the lyophilized product.

Conclusions. These 2 studies suggest that intravenous administration of VIG is well tolerated and results in a more favorable pharmacokinetic profile than does VIG administered intramuscularly.

The currently licensed smallpox vaccine (Dryvax; Wyeth Laboratories) utilizes an orthopox virus (vaccinia) that may have evolved from cowpox by serial passages of the virus in humans and animals in the 19th century. Due to its high cross-reactivity with variola, vaccinia strains have been used for smallpox vaccinations since the early 1800s. The vaccinia virus was traditionally grown on calves’ skin that had been scarified and was harvested by collecting the lymph from the pock pustules [1]. A next-generation smallpox vaccine, grown in and purified from tissue cultures, is under development [2, 3]. Since 1960, severe complications resulting from vaccination with vaccinia immune globulin (VIG) administered as an intramuscular formulation (VIGIM) [4, 5]. There are numerous reports in the literature supporting the use of VIG for the treatment and prophylaxis of smallpox vaccinia complications and for prophylaxis of those in close contact with patients with smallpox [6–15]; however, the studies evaluating the treatment of vaccinia-related complications are not controlled. Complications known to be responsive to VIG treatment include severe forms of eczema vaccinatum and progressive vaccinia [16, 17]. These are potentially fatal without VIG treatment, especially in individuals with a history of chronic atopic dermatitis, immunodeficiency (caused by treatments for HIV infection or cancer), and pregnancy [18]. Although VIGIM was previously approved by the US Food and Drug Administration, it recently returned to
An investigational new drug (IND) status and is currently available under BB-IND 8429, sponsored by the US Army. Absorption of the immune globulin from intramuscular deposits typically results in peak blood levels 3–7 days after administration [19].

A VIG formulation suitable for intravenous administration (VIGIV) offers advantages with regard to improved dosing, tolerability, and pharmacokinetic properties. It would be expected that intravenous administration of VIG would provide immediate protection against vaccinia, compared with a delayed onset of action for the intramuscular formulation. The intravenous route would also be more easily tolerated because the typical intramuscular volume for VIG is ∼42 mL for a 70-kg individual.

An effort to develop VIGIV was initiated by the US military and is underway, with the goal of licensing and stockpiling VIGIV. We conducted 2 separate studies to evaluate the safety profile and pharmacokinetic behavior of VIGIV, compared with VIGIM. The first study evaluated the safety and pharmacokinetics of a lyophilized product of VIGIV (VIGIV-lyo). Our primary objective for this study was to demonstrate that an intravenous infusion of a 100-mg/kg dose results in a serum level of vaccinia antibody 5 days after infusion that is not inferior (by as much as 20%) to the level of antibody predicted for an intramuscular injection of an equivalent dose of VIGIM at 5 days after administration (i.e., geometric mean antibody concentration [GMC] 5 days after intramuscular administration [GMC_{im}]/GMC 5 days after intravenous administration [GMC_{iv}] of <1.2).

After completion of this VIGIV-lyo study in December 2001, we decided to manufacture all previously collected plasma into a liquid product (omitting the lyophilization step) to simplify and expedite the manufacturing process. This second study evaluated the safety profile of this liquid formulation of VIGIV (VIGIV-liq).

**MATERIALS AND METHODS**

**VIG Manufacturing**

The process for the production of VIGIV is identical to that of 2 other commercial human immunoglobulin products, intravenously administered cytomegalovirus immune globulin (CMVIGIV) [20] and intravenously administered respiratory syncytial virus immune globulin (RSVIGIV) [21], except for an additional nanofiltration step to remove potential viral contaminants. Licensed plasmapheresis centers collected source plasma from US military personnel 2–78 weeks after a booster vaccination with smallpox vaccine. Figures 1A and 1B present the distribution of time intervals between booster vaccination and source plasma collection for the 2 manufacturing lots of VIGIV used in the VIGIV-lyo (lot 2) and VIGIV-liq (lot 4) studies. Donors had been previously vaccinated with smallpox vaccine >1 year before booster vaccination. All units used for the manufacturing of VIGIV were tested for the absence of hepatitis C virus (with HCV EIA, version 2.0; Abbott Laboratories), hepatitis B surface antigen, and HIV with use of commercial antibody assays. An RT-PCR assay confirmed the absence of HIV RNA in the source plasma pool. Several steps in the manufacturing process were used to ensure viral inactivation of VIGIV. These included Cohn/Oncley fractionation, nanofiltration through one 75-nm and two 35-nm filters, and solvent/detergent viral inactivation, including use of C18 column chromatography. On the basis of the size of vaccinia virus, it is very likely that vaccinia is removed by the nanofiltration steps in the manufacturing process.

Figure 1. Distribution of plasma collection time following boosting with licensed smallpox vaccine (Dryvax; Wyeth Laboratories) for source plasma units used to manufacture an intravenous formulation of vaccinia immune globulin (VIG) for use in the lyophilized product of VIG study (A) and the liquid product of VIG study (B).
Subjects
The VIGIV-lyo and VIGIV-liq studies were conducted in accordance with Good Clinical Practices and International Conference on Harmonisation guidelines and in compliance with the World Medical Association Declaration of Helsinki. We conducted both studies at the Quintiles Clinical Trials Unit in Lenexa, Kansas, after approval by the local ethics committee/investigational review board and the Human Subjects Research Review Board (the US Army’s investigational review board for the Department of Defense-sponsored clinical research). All study subjects gave written informed consent before participating in the study. For both studies, the inclusion/exclusion criteria were identical, and all subjects were ≥18 years old. All enrolled subjects met all of the inclusion and none of the exclusion criteria (table 1).

For the VIGIV-lyo pharmacokinetic and safety study, a total of 78 volunteers (55 men and 25 women) completed the study according to the protocol. Sixty-eight subjects were white, 7 were Asian, 1 was African American, and 2 were of other races. The mean body mass index (BMI) was 23.9 kg/m². For the VIGIV-liq safety study, a total of 33 volunteers (16 men and 17 women) completed the study. Twenty-six subjects were white, 1 was Asian, 4 were African American, and 2 were Hispanic. The mean BMI was 23.9 kg/m².

Study Designs
The VIGIV-lyo study was an open-label, ascending-dose, single-center, phase 2B study involving 78 healthy volunteers. Subjects were sequentially assigned to 1 of the 3 dose groups of 26 volunteers each and received VIGIV-lyo administered as an intravenous infusion at 100 mg/kg (2 mL/kg), 200 mg/kg (4 mL/kg), or 500 mg/kg (10 mL/kg). Subjects were closely monitored for safety, and we evaluated the change of the antivaccinia antibody concentration over time in each group. Serum samples for the determination of VIG titers were obtained at 5 min before starting the infusion and at 5 min, 8 h, and 2, 3, 5, 10, 14, 21, 28, 35, and 42 days after completion of infusion. Safety evaluation included recording of adverse events and obtaining blood and urine samples on days 2, 5, 21, and 42 for complete blood cell count, routine serum chemistry, and urinalysis.

The VIGIV-liq study was an open-label, single-center, phase 1 study involving 33 healthy subjects. Subjects received VIGIV-liq administered as an intravenous infusion at 100 mg/kg (2 mL/kg). The design was similar to that of the VIGIV-lyo study except that the pharmacokinetic analyses of plaque reduction neutralization (PRN) titers were not performed.

PRN Assay
The PRN assay was used to measure antibodies specific to vaccinia virus in serum samples. Clinical specimens were heat inactivated at 56 °C for 30 ± 3 min. Vaccinia virus, diluted to a predetermined level of 1000 plaque-forming units (PFU)/mL, was added to dilutions (1:5 to 1:2560) of serum and incubated for 90 ± 5 min at 36°C ± 2°C. Samples of the serum/virus mixture in 200-μL volumes were inoculated in triplicate on Vero 76 cells plated in 6-well dishes. Following an adsorption period of 60 ± 6 min at 36°C ± 2°C, the inoculated cells were overlayed with an agarose/culture medium mixture and incubated at 36°C ± 2°C until plaques developed (48 ± 6 h). A second agarose overlay containing the vital stain neutral red was then added to each well to help visualize the plaques. Each assay included virus without antibody (as a negative control), test serum without virus, and virus with a known high- or low-titer control serum (2 positive controls). The neutralization titers were reported as the calculated dilution of serum that elicited a decrease in the number of virus plaques by 50% (PRN50) and 80% (PRN80). The validated lower limit of quantitation (LOQ) was 20 U/mL for 50% reduction. All samples for a given subject were analyzed in a single run to minimize variability.

Pharmacokinetic and Statistical Analysis
We used only serum VIG concentrations equal to or greater than the qualified limit of quantitation (LOQ) of the assay in the pharmacokinetic analyses. Concentrations less than LOQ prior to the time at which maximal serum concentration (Cmax)
is achieved were set equal to 0, and concentrations less than 
LOQ after C_{\text{max}} were set to “missing.”

**Estimation of the serum concentration of VIGIM 5 days 
after intramuscular injection.** We calculated the serum concentration (C_{p}) of VIG that would be achieved 5 days after an 
intramuscular injection of 100 mg/kg using the following equation:

\[
C_{p} = \frac{k^{0} (1 - \exp^{-k_{l}T})}{\lambda_{z}V_{z}} ,
\]

where \(k^{0}\) is the zero order input rate, \(\lambda_{z}\) is the first order elimination rate constant, \(V_{z}\) is the total apparent volume of distribution per kilogram of body weight (intravascular and extravascular volume), and \(T\) is the duration of the input [22]. This assumes that absorption from the muscle is zero order and no catabolism occurs in muscle tissue.

The currently measured PRN titer of VIGIM is 1:5343, which is the geometric mean titer (GMT) of 7 individual results, each calculated by determining the GMT of samples run on the same day (3 samples per day, except for 1 day with 1 sample). This is expressed in dimensionless “arbitrary units” (AU) as 5343 AU/mL. A 100 mg/kg dose corresponds to 0.6 mL/kg of VIGIM, for a total IgG dose of 5343AU/mL \(\times\) 0.6 mL/kg = 3206 AU/kg. Each subject’s input rate, \(k^{0}\), was calculated using his or her body weight according to the following formula:

\[
k^{0} = \frac{\text{Dose}}{T} = \frac{3206 \text{ AU/kg} \times \text{Weight}}{5 \text{ Days}} .
\]

Values for \(\lambda_{z}\) and \(V_{z}\) for each subject were estimated from the subject’s body weight and hematocrit value (HCT) assuming a blood volume of 70 mL/kg and using consensus values for the elimination half-life (\(t_{1/2}\)) of IgG (22 days) and the ratio of intravascular volume (IVV) to \(V_{z}\) (0.45) [22] using the formulae:

\[
\lambda_{z} = \frac{0.693}{22 \text{ Days}} = 0.0315 \text{ Days}^{-1} ,
\]

\[
IVV = 70 \text{ mL/kg} \times \text{Weight} \times (1 - \text{HCT}) ,
\]

\[
V_{z} = \frac{IVV}{0.45} .
\]

**Noncompartmental pharmacokinetic analysis.** The C_{\text{max}} and time to C_{\text{max}} (T_{\text{max}}) are determined directly from the data. The first order elimination rate constant, \(\lambda_{z}\), was defined as the negative of the slope of the terminal log-linear portion of the serum concentration time curve. Areas under the serum concentration time curve to infinity (AUC) and first moment (C \(\times\) t vs. t) (AUMC) were calculated using the linear trapezoidal method to the last time point (\(t_f\)) with a concentration above the qualified limit of quantitation (AUC_{\text{LOQ}} , AUMC_{\text{LOQ}}) with extrapolation to infinity according to [23]:

\[
\begin{align*}
\text{AUC}_{\infty} &= \text{AUC}_{p-1} + \frac{C_{\text{p}}}{\lambda_{z}} , \\
\text{AUMC}_{\infty} &= \text{AUMC}_{p-1} + \frac{t_{f} \times C_{\text{p}}}{\lambda_{z}} + \frac{C_{\text{p}}}{\lambda_{z}^{2}} .
\end{align*}
\]

Total serum clearance (CL), \(V_{z}\), and volume of distribution at steady state (\(V_{ss}\)) were calculated according to the following formulae:

\[
\begin{align*}
\text{CL} &= \frac{\text{Dose}}{\text{AUC}_{\infty}} , \\
\text{V}_{z} &= \frac{\text{Dose}}{\lambda_{z} \times \text{AUC}_{\infty}} , \\
\text{V}_{ss} &= \frac{\text{Dose} \times \text{AUMC}}{\text{AUC}^{2}} - \frac{\text{Dose} \times T}{2 \times \text{AUC}} ,
\end{align*}
\]

where \(T\) is the duration of infusion.

**Comparison of observed intravenous and predicted intramuscular concentrations.** GMC_{\text{IM}} and GMC_{\text{IV}} are the geometric mean antibody concentrations 5 days after intramuscular and intravenous administration, respectively. The null hypothesis stated that the ratio of GMC_{\text{IM}} / GMC_{\text{IV}} is \(\geq\)1.2 (i.e., the GMC is \(\geq\)20% higher after intramuscular administration than after intravenous administration). This hypothesis was tested using a paired t test of the differences between logarithms of observed antibody levels after VIGIM administration and predicted antibody levels after VIGIM administration. A 2-sided 95% CI for the ratio GMC_{\text{IM}}/GMC_{\text{IV}} was estimated from the corresponding 95% CI for the mean difference between logarithms. NCSS software, version 2002 (Number Cruncher Statistical Systems), was used to perform the statistical analyses.

**Comparison of VIGIV pharmacokinetic parameters among doses.** Pharmacokinetic parameters dependent upon dose—AUC_{\text{p-1}} and AUC_{\infty}—were compared using the natural logarithms of the data and an analysis of variance model with dose as the only classification variable. Values for the 100-mg/kg and 500-mg/kg doses were normalized to 200 mg/kg before analysis. Parameters not dependent upon dose—CL, \(V_{z}\), and \(t_{1/2}\)—were compared among doses using the same analysis of variance model but without logarithmic transformation of the data.
Cmax is a function of both dose and the duration of the infusion. Because the duration of infusion differed among doses, comparison between doses could not be made for Cmax.

The relationship between AUC0–t, the area under the curve; CL, clearance; Cmax, maximum concentration; NA, not applicable; T max, time at which maximum concentration is reached; t 1/2, half life; V ss, volume of distribution at steady state; V z, volume of distribution.

NOTE. Data are mean value ± SD, unless otherwise indicated. None of the parameters were normalized, and all were analyzed on the original scale, unless otherwise indicated. AU, arbitrary units; AUC0–t, area under the curve when serum antibody is detectable; AUCmax, total area under the curve; CL, clearance; Cmax, maximum concentration; NA, not applicable; Tmax, time at which maximum concentration is reached; t1/2, half life; Vss, volume of distribution at steady state; Vz, volume of distribution.

Table 2. Pharmacokinetic parameters for vaccinia immune globulin after intravenous infusion of 100 mg/kg, 200 mg/kg, or 500 mg/kg to healthy volunteers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose group</th>
<th>P b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg/kg (n = 25)</td>
<td>200 mg/kg (n = 26)</td>
</tr>
<tr>
<td>Cmax, AU/mL</td>
<td>255 ± 143</td>
<td>481 ± 208</td>
</tr>
<tr>
<td>Tmax, median h (range)</td>
<td>1.28 (1.13–46.8)</td>
<td>1.93 (1.92–44.4)</td>
</tr>
<tr>
<td>AUC0–t, h × AU/mL</td>
<td>62,465 ± 32,656</td>
<td>133,937 ± 41,188</td>
</tr>
<tr>
<td>AUCss, h × AU/mL</td>
<td>84,566 ± 47,280</td>
<td>171,727 ± 55,096</td>
</tr>
<tr>
<td>CL, mL/h/kg</td>
<td>0.095 ± 0.048</td>
<td>0.082 ± 0.030</td>
</tr>
<tr>
<td>Vss, mL/kg</td>
<td>64.5 ± 24.1</td>
<td>62.3 ± 36.9</td>
</tr>
<tr>
<td>Vz, mL/kg</td>
<td>61.7 ± 24.6</td>
<td>60.4 ± 35.1</td>
</tr>
<tr>
<td>t1/2, h</td>
<td>519 ± 157</td>
<td>523 ± 197</td>
</tr>
</tbody>
</table>

Pharmacokinetics of Intravenous VIG

The mean serum VIG concentrations are illustrated in figure 2. The mean pharmacokinetic parameters are summarized in table 1. The mean values and ranges across the 3 doses tested for Vss (68.7 mL/kg; range, 28.6–175 mL/kg) and t½ (21.6 days; range, 11.1–42.2 days) are consistent with the consensus values of 86 mL/kg (assumes IVV = 0.45 and 1 – HCT = 0.55) and 22 days, respectively, used to estimate the serum VIGIM concentrations after intramuscular administration [22]. Serum concentrations after VIGIV increase in proportion to dose. There are no significant differences among doses for any of the pharmacokinetic parameters (table 2), with the exception of AUC0–t. Log-log plots of AUC0–t and AUCss versus dose are linear, with slopes of 0.845 and 0.921, respectively.

Safety

All doses of VIGIV were well tolerated in both studies (table 3). Most adverse events were mild or moderate, except for 2 severe adverse events (headache and dysmenorrhea), each reported by 1 subject in the 100 mg/kg VIGIV-lyo group and 1 subject in the 200 mg/kg VIGIV-lyo group. There were no serious adverse events, and none of the subjects withdrew from the study due to an adverse event. Four patients had cases of urticaria that were mild-to-moderate in severity and resolved estimated to be 0.406 (95% CI, 0.339–0.485). Thus, we rejected the null hypothesis specified in the study objectives (t = −12.51 with 24 df; P < .001). We also rejected the hypothesis of equal GMCs in favor of the alternative hypothesis that GMCIV > GMCIM (t = −10.40; P < .001).
Table 3. Adverse events and treatment-related adverse events reported in >5% of subjects receiving either an intravenous infusion of a lyophilized product of vaccinia immune globulin (VIGIV-lyo) or an intravenous infusion of a liquid product of vaccinia immune globulin (VIGIV-liq).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>VIGIV-lyo</th>
<th>VIGIV-liq</th>
<th>VIGIV-lyo</th>
<th>VIGIV-liq</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500 mg/kg</td>
<td>200 mg/kg</td>
<td>100 mg/kg</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(n = 26)</td>
<td>(n = 26)</td>
<td>(n = 26)</td>
<td>(n = 33)</td>
</tr>
<tr>
<td>Reporting adverse event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10 (38%)</td>
<td>1 (4%)</td>
<td>6 (23%)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue, and bone disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (15%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

a All subjects in the VIGIV-liq group received a 100-mg/kg dose.
without treatment 1–8 h following administration. There were no marked differences among dose groups in the incidence of reported adverse events, clinical laboratory results, vital signs, electrocardiography findings, or physical examination findings.

**DISCUSSION**

Our approach to comparing the pharmacokinetics of VIGIM and VIGIV is unique, in that a direct comparison of the pharmacokinetic properties of intravenous and intramuscular formulations of VIG was made. We used consensus values to estimate selected variables required to calculate the GMCs at 5 days after a theoretical administration of VIGIM, on the basis of a method initially developed and reported by Finlayson and Tankersley in 1984 [22]. This approach allowed us to reduce the number of volunteers via elimination of a VIGIM group, which is relevant because VIGIM is currently an IND product and in limited supply. It also eliminated the need to expose healthy volunteers to a large volume of immunoglobulin, which is typically administered as a 42-mL dose in a 70-kg person.

The GMC of a 100-mg/kg dose of VIG after intravenous administration is ~2.5 times greater than that predicted for VIG when administered via the intramuscular route. In addition, VIG concentrations in serum increase approximately linearly, with increased dose levels of 100–500 mg/kg. The slopes of the log-log plots of AUC$_{0-\text{inf}}$ and AUC$_{\text{ss}}$ vs. dose are <1, probably because of different subjects were used for each dosing cohort, rather than because of nonlinear pharmacokinetics.

Adverse event rates are comparable regardless of product or dosage level (table 3). The most commonly observed adverse events in both studies were headache and nausea, and the majority of adverse events were not considered to be treatment related. Comparable adverse event rates for VIGIV doses that were 5 times the size of the target dose further support the conclusion that VIGIV is well tolerated. We anticipated that the side effects of VIGIV would be the same as those for CMVIGIM and RSVIGIV because all 3 are human source plasma-derived products and are subjected to similar immune globulin extraction and purification procedures. CMVIGIM and RSVIGIV are typically given in doses of 50–150 mg/kg and 750 mg/kg, respectively [20, 21]. The majority of reactions experienced with these products occur during infusion, are mild, and usually respond to decreasing the infusion rate or stopping the infusion. CMVIGIM is used in solid-organ transplantation for the prophylaxis of cytomegalovirus disease. Clinical trials reported that reactions such as flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing were the most frequent adverse reactions, observed at a frequency of <56% of all infusions [20]. RSVIGIV is used to prevent serious lower respiratory tract infection caused by RSV in children <2 years of age with bronchopulmonary dysplasia or a history of premature birth. Clinical trials in this setting suggest that adverse events are uncommon and comparable to placebo [21]. Azotemia, oliguria, and anuria have been observed with other immunoglobulin products [24–26]. Rare side effects are severe allergic reactions, aseptic meningitis, and the theoretical risk for transmission of blood-borne pathogens [5, 19]. The effects of VIGIV in pregnant women are unknown. However, other intravenous immunoglobulin products are listed as pregnancy category C, indicating that risk to the fetus cannot be ruled out [20, 21].

The intravenous infusion of VIG provides a safe and well-tolerated route of administration. The higher GMCs in subjects after administration of VIGIM, compared with VIGIM, support a preference of this product over the existing VIGIM investigational product.

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**Conflict of interest.** R.J.H., M.A., and S.W.-L. are employees of Dynport Vaccine; W.K. and W.B. are Dynport Vaccine consultants. G.B. is a Baxter Healthcare employee. All other authors: No conflict.

**References**