Hemolytic events after the administration of lyophilized versus liquid immune globulin: an analysis of a single manufacturer's safety database

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BACKGROUND: Recent publications have raised concerns that liquid immune globulins (IGs) may be associated with either a higher or a lower frequency of hemolytic events compared to lyophilized IGs, among other reasons due to the differences of their isohemagglutinin content. The aim of this study was to evaluate the relationship of hemolytic events to product presentation (liquid versus lyophilized) and to examine the relationship between total IG doses administered and the individual isohemagglutinin titers of IG lots infused.

STUDY DESIGN AND METHODS: The reporting rate as well as the proportional reporting rate (PRR) of hemolytic events for liquid (Gammagard liquid [GGL]) and lyophilized IG (Gammagard S/D [GGSD]) received spontaneously from the United States was calculated. For all hemolytic events received spontaneously from global sources, total IG doses (g/kg body weight) and the loading dose of isohemagglutinins (total IG dose infused $\times$ isohemagglutinin titers of infused lots) were determined.

RESULTS: With 0.27 and 0.33 cases per 1 million grams distributed, the reporting rates for GGL and GGSD are comparable, further confirmed by a PRR of 1.0 (95% confidence interval, 0.4-2.7). Hemolytic events for GGL and GGSD were observed with low loading doses of isohemagglutinins, and lots with high isohemagglutinin titers did not contribute to the development of hemolytic events in a higher proportion than lots with low titers

CONCLUSIONS: Hemolysis associated with GGL or GGSD can occur even with low loading doses of isohemagglutinins. Data presented do not indicate that high isohemagglutinin titers of IG products play a major role in the development of these events.

Intravenous (IV) immune globulins (IGs) have been in clinical use since the 1960s;[1] since then, the global IVIG consumption has steadily grown from approximately 300 kg in 1980 to more than 100 tons in 2010.[2] While initially used for replacement therapy in immune-deficient patients, IVIG was soon recognized as being efficacious in idiopathic thrombocytopenic purpura, and subsequently the effect of IVIG therapy was studied for the treatment of numerous other diseases.[3] Exemplifying the broad range of conditions for which IVIGs are being used today, the Australian criteria for the clinical use of IVIGs, for example, list 32 conditions for which IVIGs have either an established or an emerging therapeutic role and 29 additional conditions where they may be used in exceptional circumstances.[4]

Hemolytic events associated with IVIG therapy have been long recognized as adverse events (AEs) of treatment,[5] with risk factors such as high-dose treatment ($\geq$2 g/kg body weight) and patients with non-O blood group appearing to play a role in their development.[6] In addition, the varying content of isohemagglutinins in IVIG preparations has been identified as a potential product-related risk factor.[7] While biologically plausible, the role of

ABBREVIATIONS: AE(s) = adverse event(s); GGL = Gammagard liquid; GGSD = lyophilized Gammagard; IG(s) = immune globulin(s); IVIG = intravenous IG; PID = primary immunodeficiency; PRR = proportional reporting ratio; SRS(s) = spontaneous reporting scheme(s).

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these risk factors as well as the underlying pathomechanism for the development of IG-associated hemolysis are not fully understood. In a recently published case series an increased frequency of hemolytic events after treatment with liquid compared to lyophilized IVIG preparations was observed and deemed to be related to a higher isohemagglutinin titer in liquid IVIGs.[8] Such case series typically include only few cases of hemolysis, reported for multiple IGs with different formulations, thereby limiting the possibility to detect potential product-specific differences with regard to the development of these events. The a priori assumption that all IGs have a similar safety profile is misleading as various factors such as diluent composition, impurity levels, and manufacturing process can result in unique differences affecting the product's safety profile.[9] Furthermore, in contrast to a case series describing higher rates of hemolysis for liquid IVIGs, a recent claims-based study observed a potentially elevated risk of same-day hemolytic events for lyophilized IGs compared to a reference liquid IVIG.[10]

The aim of this retrospective review of a single manufacturer's safety database was to evaluate the relationship between hemolytic events and product presentation (lyophilized vs. liquid IG). In addition, all spontaneous AE reports of hemolytic events received globally for these two IGs were analyzed to examine the relationship between the total IG dose administered and the individual anti-A and anti-B isohemagglutinin titers of IG lots infused.

MATERIALS AND METHODS

Baxter's global pharmacovigilance safety database was reviewed for all spontaneously reported AEs received for liquid IG (Gammagard liquid [GGL]; in countries outside North America, GGL is marketed with the brand name Kiovig) and lyophilized IG (Gammagard S/D [GGSD]), regardless of mode of IG administration (IVIG or subcutaneous [SC]IG administration), between January 1, 2006, and December 31, 2013. Case reports of potential hemolytic events were identified with the Standardised MedDRA Query (SMQ) "haemolytic disorders" of the Medical Dictionary for Regulatory Activities (MedDRA).[11] For spontaneously reported cases of hemolysis from the United States, reporting rates (cases per 1 million grams distributed) and the proportional reporting ratio (PRR) for GGSD versus GGL were calculated. For the PRR the statistical association was tested with the chi-square test on one degree of freedom with Yates's correction. The PRR as a measure of disproportionate reporting is calculated from a two-by-two table, where the PRR is $A/(A+C)$ divided by $B/(B+D)$. For this study, A represents the event of interest (i.e., case reports of hemolysis) for GGSD, B the event of interest for GGL, C all other case reports (i.e., excluding reports of hemolysis) received for GGSD, and D all other case reports received for GGL. The expected (null) value for PRR calculations is 1; the higher the PRR, the greater the strength of a signal. For pharmacovigilance purposes, when generating signals from spontaneous reporting, it has been suggested that a signal of disproportionate reporting can be assumed when the PRR is at least 2 and chi-squared is at least 4 (and three or more cases of interest have been reported).[12]

Distribution data for GGL and GGSD were obtained from Baxter's finance database systems. Total doses of GGL and GGSD (g/kg body weight) were calculated for those AE reports of hemolytic events, which included the required data. Production records were reviewed to determine the anti-A and anti-B isohemagglutinin titers of all GGL and GGSD lots manufactured between January 1, 2006, and December 31, 2013. Isohemagglutinin titers were determined with either the indirect or the direct test method according to the European Pharmacopoeia[13] and were performed on the final product in Baxter's Quality Control Laboratory before market release.

Isohemagglutinin titer values alone do not permit an estimate of the absolute amount of antibody exposure of patients who experienced hemolytic events. Therefore, for all AE reports of hemolysis that included both lot numbers and the total IG dose administered, the loading dose of isohemagglutinins was calculated as a surrogate variable (total dose $\times$ titer value). For patients who had received multiple lots during the last treatment cycle before a hemolytic event, the lot with the highest titer value was used for this calculation.

RESULTS

US reporting trend for GGL and GGSD

In the United States, the distribution of GGL steadily increased from approximately 4.5×10^6 g in 2006 to more than 17×10^6 g in 2013, while the distribution of GGSD steadily decreased from nearly 4×10^6 g in 2006 (with a peak of more than 5×10^6 g in 2007) to nearly 0.8×10^6 g in 2013. In total, between January 1, 2006, and December 31, 2013, nearly 96×10^6 g of GGL and more than 15×10^6 g of GGSD were distributed in the United States (Table 1). US distribution data accounted for approximately 75% of their global distribution in these 8 years.

During this period, a total of 1552 spontaneous AE reports for GGL and 313 spontaneous AE reports for GGSD were received from the United States alone, excluding solicited reports and reports from literature. Searching these 1865 AE reports with MedDRA SMQ "haemolytic disorders" resulted in the identification of 26 hemolytic events identified for GGL, and five hemolytic events for GGSD, which is a reporting rate of 0.27 and 0.33 cases per 1 million g distributed, respectively, for the two products (Table 1). No hemolytic event was reported for SC administrations of GGL or GGSD.

TABLE 1. GGL and GGSD usage, number of hemolytic AE reports, and reporting rates from January 1, 2006, through December 31, 2013, in the United States

	GGL (liquid IG)	GGSD (lyophilized IG)
IG distribution (g) (both IVIG and SCIG)	95,801,324	15,321,103
Hemolytic AE reports	26	5
Hemolysis reporting rate (cases per 1 million grams distributed)	0.27	0.33
PRR (95% CI) for GGSD vs. GGL	1.0 (0.4-2.7)	

The PRR for the analyzed spontaneous US case reports of hemolysis for GGSD versus GGL was 1.0 (95% confidence interval [CI], 0.4-2.7), with chi-square (Yates corrected) calculated at 0.02 ($p = 0.89$), indicating that no increased risk of experiencing a hemolytic event after therapy with either GGSD or GGL can be observed.

GGL and GGSD dosing regimens associated with hemolytic events reported globally

For GGL and GGSD a total of 89 spontaneous AE reports of hemolytic events were received globally between January 1, 2006, and December 31, 2013 (80 events reported for GGL and nine events reported for GGSD), including solicited reports and reports from literature. As in the United States, no hemolytic event occurred after SC administration of GGL or GGSD. Of the 89 hemolytic events, only two were reported for patients with primary immunodeficiency (PID), both of which had occurred after therapy with GGSD.

For GGL, the total dose (g/kg body weight) administered per treatment cycle was available for 37 of 80 (46%) hemolytic events, and for GGSD this information was available for four of nine (44%) hemolytic events (Table 2). Data presented in Table 2 indicate that 95% of hemolytic events associated with GGL had occurred in dosing regimens of at least 1 g/kg body weight. Given the low number of events reported for GGSD, no clear corresponding trend can be observed.

TABLE 2. Number of hemolytic events (received globally) per total IG dose (g/kg body weight)

Total dose (g/kg body weight)	Hemolytic events with GGL (liquid IG)	Hemolytic events with GGSD (lyophilized IG)
<0.5	2	0
0.5 to <1.0	0	2
1.0 to <2.0	13	1
2.0 to <3.0	12	0
3.0 to <4.0	6	0
≥4.0	4	1
Total	37	4

Anti-A and anti-B isohemagglutinin titers for finished GGL and GGSD lots

A total of 2769 lots of GGL were manufactured between January 1, 2006, and December 31, 2013, and 563 lots of GGSD. Absolute titer values for all manufactured lots of both products are displayed in Fig. 1, with the exception of 66 GGL lots and 30 GGSD lots, for which no absolute titer values were determined (these lots were tested with the direct method, but the results were only recorded as "satisfactory," i.e., titer values of not more than 64, thereby meeting the specifications of the European Pharmacopoeia). As shown in Fig. 1, anti-A and anti-B isohemagglutinin titers of finished GGL lots were higher compared to GGSD.

Total IG dose and anti-A and anti-B isohemagglutinin loading doses for hemolytic events reported globally

To examine the relationship between the total IG dose administered and the individual anti-A and anti-B isohemagglutinin titers of infused lots, the total dose administered multiplied with the anti-A and anti-B isohemagglutinin titer was calculated as a surrogate variable of the total anti-A and anti-B isohemagglutinin loading dose for all hemolytic AE reports associated with GGL for which a corresponding lot number was reported (Table 3). Other than expected, the frequency of hemolytic events did not increase with increased loading doses of isohemagglutinins. The largest proportion of hemolytic events was seen in patients receiving the lowest isohemagglutinin loading doses. Of the total 33 hemolytic AEs reported in adults, 39% (10/33) and 69% (21/33) of adults, respectively, experienced hemolytic events with a total anti-A and anti-B isohemagglutinin loading dose of not more than 1000 (Table 3). Similarly, of the total 12 hemolytic AEs reported in children, 83% (10/12) and 92% (10/12), respectively, experienced the hemolytic events with a total anti-A and anti-B isohemagglutinin loading dose of not more than 1000 (Table 3).

For GGSD, only two hemolytic AE reports were received that included information on lot numbers. The corresponding loading doses (anti-A and anti-B isohemagglutinins) were calculated with 320 and 80 in one case

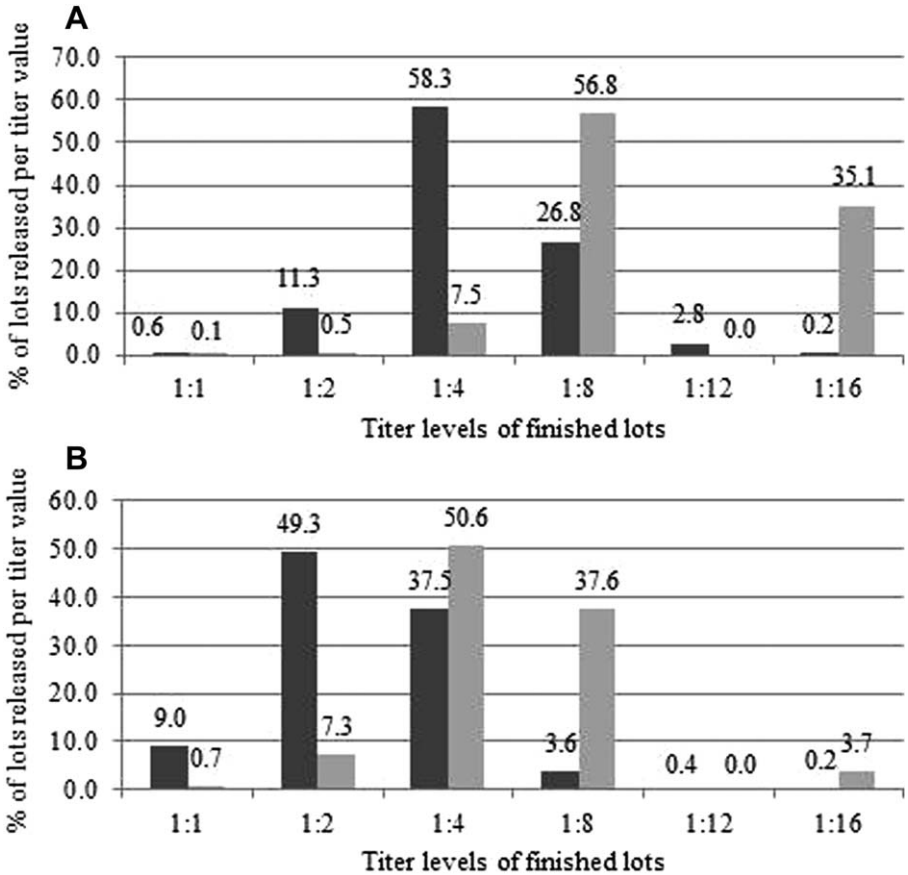

Fig. 1. Isohemagglutinin titers (%) of all manufactured GGL (gray) and GGSD (black) lots (excluding 66 GGL lots and 30 GGSD lots that were tested as "satisfactory," but without corresponding titer values): (A) anti-A isohemagglutinin titers; (B) anti-B isohemagglutinin titers.

(referring to a 12-year-old boy treated for thrombotic thrombocytopenic purpura) and 120 and 60 for the other case (referring to a 59-year-old female treated for IgG subclass deficiency [IgG2, IgG4] and IgA deficiency with IgM deficiency).

GGL and GGSD lots associated with hemolytic events reported globally

For GGL, 54 of 80 AE reports of hemolysis from global reporting included lot numbers, and a total of 110 GGL lots were associated with these 54 hemolytic events (i.e., 17 hemolytic events had occurred after the infusion of a single lot, and the remaining 37 events after the infusion of multiple lots). For GGL, the percentage of lots manufactured with a given anti-A and anti-B isohemagglutinin titer compared to the 110 lots associated with hemolytic events are displayed in Fig. 2.

For GGSD, two of nine AE reports of hemolysis from global reporting included information on lot numbers. One hemolytic event followed the infusion of a single lot (anti-A titer value, 4; anti-B titer value, 2), and one hemolytic event followed the infusion of two lots (anti-A titer values, 8 and 4; anti-B titer values for both lots, 2).

With respect to patient exposure to lots with given isohemagglutinin titer values, hemolytic events with GGSD occurred in a frequency comparable to the percentage of hemolytic events that occurred with finished GGL lots. As in the United States, global reporting of hemolytic events with finished lots that had high isohemagglutinin titers was not disproportionately high.

DISCUSSION

This review presents a head-to-head comparison of hemolytic events spontaneously received over an 8-year time period for a liquid versus a lyophilized IG. In contrast to a published case series[8] and a claims-based study,[10] the rate of hemolytic events reported for lyophilized IG (GGSD) is comparable to the rate reported for liquid IG (GGL) when analyzing data from spontaneous AE reporting (0.27 vs. 0.33 hemolytic events, respectively, reported per million grams of GGL and GGSD distributed). A PRR of 1.0 (95% CI, 0.4-2.7) calculated for the spontaneous US

TABLE 3. Number of hemolytic events associated with GGL (reported globally) per anti-A and anti-B isohemagglutinin loading doses seen in adults and children

	Events of hemolytic AEs associated with the given isohemagglutinin loading dose			
	Anti-A		Anti-B	
Loading dose [(total dose) × (antibody titer of infused GGL lot)]	Adults (age range, 23-86 years; loading dose range, 80-4800)	Children (age range, 0-14 years; loading dose range, 26-1600)	Adults (age range, 23-86 years; loading dose range, 40-4800)	Children (age range, 0-14 years; loading dose range, 6.5-1440)
0-250	6	5	8	7
>250-500	2	3	6	3
>500-750	2	2	7	0
>750-1000	3	0	2	1
>1000-2000	10	2	7	1
>2000-3000	6	0	2	0
>3000	4	0	1	0
All	33	12	33	12

case reports of hemolysis for GGSD versus GGL confirms the absence of disproportionate reporting of hemolytic events with IGs, thus providing greater confidence that the reported rates for the two products are indeed comparable.

GGL lots are manufactured with higher anti-A and anti-B titers compared to GGSD, which is consistent with previous publications on the isohemagglutinin content of liquid versus lyophilized IGs.[14] Comparing lots associated with hemolytic events to the percentage of all lots manufactured with given isohemagglutinin titers, it is apparent that lots with high isohemagglutinin titers did not contribute to the development of hemolytic events in a higher proportion than lots with low titers. Most of the hemolytic events occurred in disorders treated with high doses of IVIG, and only in 5% of events were observed with total IVIG doses of less than 0.5g/kg bodyweight, confirming previously published data.[6]

When calculating isohemagglutinin loading doses, the results of this study indicate that hemolytic events are not restricted to high loading doses of isohemagglutinins. Partially similar results have been reported for plasma-incompatible platelet transfusions; Karafin and colleagues[15] reported that while plasma compatibility is an important factor for predicting hemolysis, ABO antibody titers are of limited value in predicting hemolytic reactions. They observed a greater risk of hemolysis with both increasing ABO antibody titers and the volume of plasma-incompatible transfusions, which in this combination was not observed in this study.

For both GGL and GGSD, hemolytic events can be observed with low loading doses of isohemagglutinins. These doses can be theoretically calculated for dosing regimens typical for the treatment of PID and other low-dose indications. With PID patients using at least 15% of all IVIG in the United States,[16] it is surprising that PID patients with a report of a hemolytic event are significantly underrepresented with only 2% reporting such an event. The absence of hemolytic events in PID patients was also observed in clinical trials with intravenously administered GGL.[17,18]

Reasons for a disproportionately fewer number of PID patients having a hemolytic event cannot be determined given the retrospective nature of this study. One speculation for why hemolysis is underrepresented in low-dose IG regimens such as PID could be that a greater percentage of patients receive SCIG infusions rather than IVIG, as indicated by a recent report.[19] Another explanation may be similar to what Markvardsen and coworkers[20] suggest; that is, immunization to blood type ABO antibodies could occur during maintenance therapy with IVIGs. But these authors failed to demonstrate a significant difference between de novo and maintenance therapy, although a clear trend in favor of a less severe hemolytic reaction after maintenance therapy could be observed.

The analysis of data from spontaneous reporting schemes (SRSs), as done in this study, bears multiple limitations. It is important to emphasize that the reporting rates presented in this study do not equal incidence rates; incidence rates cannot be calculated from spontaneous data, and in SRS underreporting of AEs is deemed to exceed 80%.[21] However, reporting rates can serve as indicators for safety signals, including significant differences in the magnitude of a risk when comparing products, or support their absence as demonstrated in this retrospective review.[22] Ideally, replacing the use of distribution data and reporting rates with actual usage data as obtained from claims-based studies would negate the need for some of the assumptions made when interpreting data from SRS. Unfortunately, today the identification of individual products in claims databases is limited, as corresponding codes are not available for every brand, and the possibility of misclassifications needs to be further evaluated.[10]

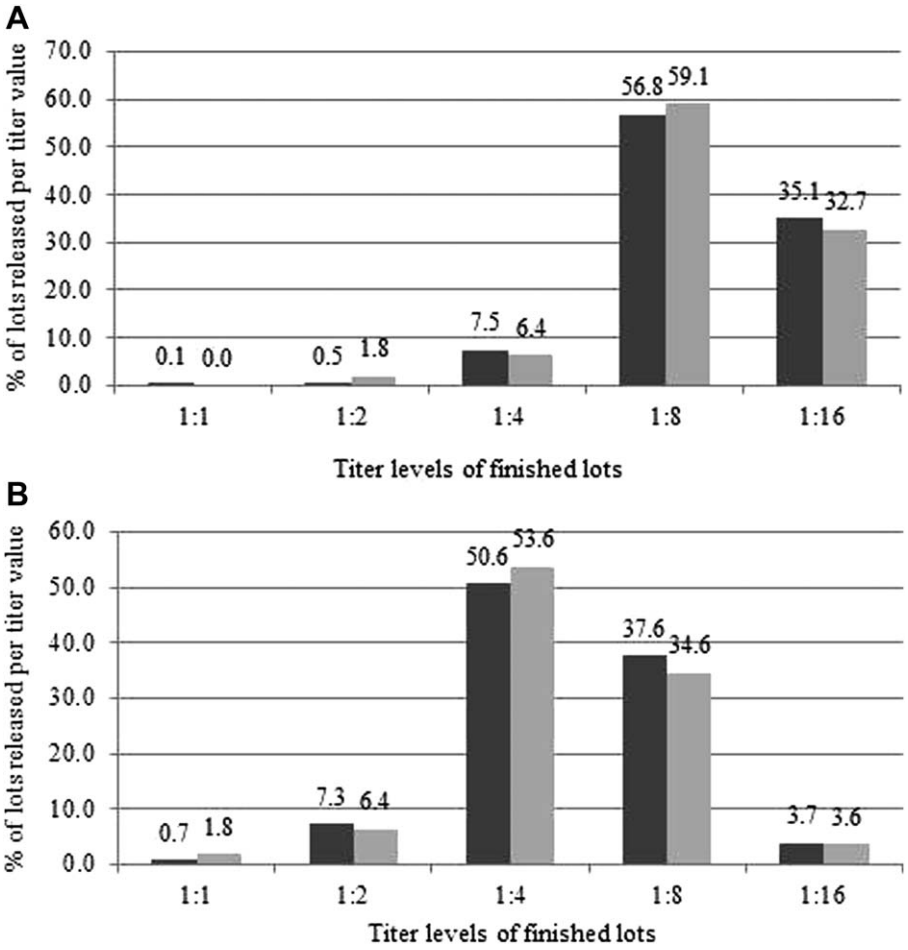

Fig. 2. Isohemagglutinin titers (%) of all GGL lots manufactured (black) versus lots associated with hemolytic events (gray, global data): (A) anti-A isohemagglutinin titers; (B) anti-B isohemagglutinin titers.

Another important limitation of SRS is the presence of incomplete data. In this study, 65 (73%) of a total of 89 identified AE reports of hemolytic events received globally included information of the total IG dose administered, 56 (63%) reports of hemolytic events were reported with a lot number, and even fewer (41 reports [46%]) allowed calculating the total IG dose/kg body weight administered. This limitation also affected the calculation of the presented isohemagglutinin loading doses. If multiple IG lots had been administered during a treatment course, the loading dose was calculated by multiplying the total dose administered during the treatment course with the anti-A or anti-B isohemagglutinin titer of the lot with the highest titer value, as the data content of most AE reports did not allow to identify the individual dose(s) with which each lot had contributed to the total dose. Therefore, some of the loading doses presented may actually have been lower than shown in Table 3, but this systematic limitation would have only shifted the presented results to the lower end of the loading dose range. Thus, the overall finding that IG-associated hemolysis can occur at every loading dose level (including especially low loading doses) would not have been affected. The fact that this limitation does not appear to affect the overall conclusion can be further demonstrated when examining the loading doses for hemolytic events that had occurred after the infusion of a single lot of GGL: In 14 cases of hemolytic events for which a loading dose could be calculated, the majority occurred with low loading doses (Fig. 3).

These limitations also highlight that AE reporting by physicians and other health care professionals could be further improved, possibly by fostering their understanding of the value of spontaneous reporting.[23] The perceived burden of AE reporting needs to give way to the recognition that this type of safety reporting ensures the real-time surveillance of medicinal products, particularly needed for biologics used in rare disorders where low absolute numbers of AE reports make interpreting spontaneous AEs a challenging task.[24]

In summary, available pharmacovigilance data for GGL and GGSD do not support observations that liquid IGs are associated with either higher or lower rates of

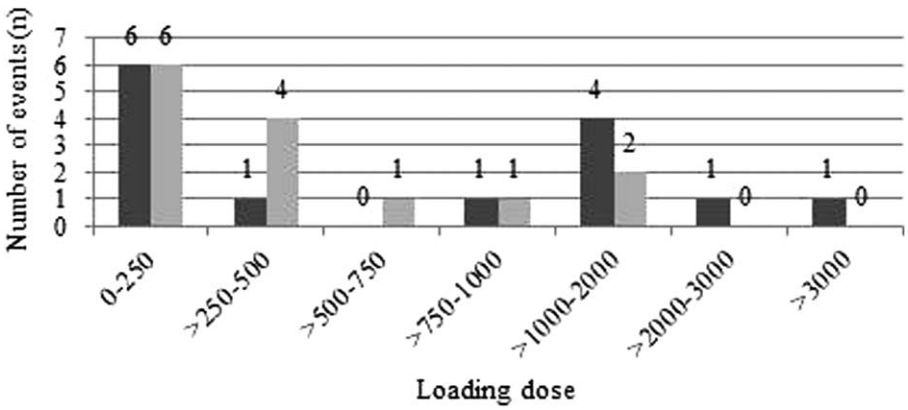

Fig. 3. Anti-A (black; range, 26-3360) and anti-B (gray; range, 6.5-1680) isohemagglutinin loading doses (total dose × titer value) for hemolytic events after the infusion of a single GGL lot (global data).

hemolysis compared to lyophilized IGs. Furthermore, these data suggest that hemolysis associated with one of these two products can occur even with low loading doses of isohemagglutinins, thus questioning the theory that absolute isohemagglutinin titers play a major role in the development of these events and consequently questioning the hypothesis that lowering of isohemagglutinin titers will result in the reduction of the rate of observed IG-associated hemolytic events.

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CONFLICT OF INTEREST

All authors are employees of Baxter Innovations GmbH or Baxter Healthcare Corp., the marketing authorization holder of Gammagard Liquid and Gammagard S/D. RB and DJ are shareholders of Baxter Healthcare Corp.

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