Acute Hemolysis After High-Dose Intravenous Immunoglobulin Therapy in Highly HLA Sensitized Patients

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Background and objectives: Intravenous Ig (IVIG) is used in renal transplantation for desensitization and treatment of antibody-mediated rejection (AMR). The infusion of high-dose IVIG is generally well tolerated, but there are reports of hemolytic anemia induced by anti-blood group antibodies present in IVIG. Here, we report our experience with IVIG-induced hemolytic anemia (IH) in ESRD patients receiving IVIG for desensitization or treatment of AMR.

Design, setting, participants, & measurements: All patients receiving IVIG for desensitization or for treatment of AMR were monitored for evidence of acute anemia and hemolysis. Markers of hemolysis, including direct antiglobulin tests, were recorded. Five different IVIG products were tested for isohemagglutinin titers.

Results: There were 18 cases of IH in 16 patients. All identified cases received the IVIG product Gamunex, Gammagard liquid, or Privigen. All patients developing hemolysis were non-O blood types. Isohemagglutinin titers ranged from 1:2 to 1:64 in the various IVIG products, with higher titers noted in the liquid, nonlyophilized products.

Conclusions: Acute IH is a significant complication of high-dose IVIG infusion. Identified risk factors include non-O blood type of the recipient and administration of liquid IVIG preparations with high titer anti-A/B IgG antibodies. We recommend monitoring hemoglobin 48 to 72 h after IVIG infusion. If the hemoglobin decreases, a hemolytic work-up is recommended. Hemolysis could be avoided in at risk patients by choosing a low titer product. However, other complications such as acute renal failure or thrombosis may be seen because the low titer products are usually hyperosmotic.

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Intravenous Ig (IVIG) was initially used to treat primary immune deficiencies. Low-dose IVIG, 0.2 to 0.6 g/kg, has been used safely for the treatment of these disorders (1). IVIG is now used in higher immunomodulatory doses for the treatment of various autoimmune, inflammatory, and infectious diseases (2-4). For transplant recipients, IVIG has become the mainstay of therapy to desensitize highly HLA-sensitized patients and to treat antibody mediated rejection (AMR). It is also used in the treatment of polyomavirus and parvovirus disease (5,6). The infusion of IVIG products is usually well tolerated. Some common side effects of IVIG infusion include pyrexia, rigors, and headache (7). Rare, but significant, adverse events include acute kidney injury related to sucrose induced osmotic nephropathy, hypersensitivity reactions, and vascular thrombosis (7,8). Our group has extensive experience with the use of IVIG products in highly HLA-sensitized ESRD patients on dialysis and renal allograft recipients with AMR. The overall safety profile of selected products has been extensively studied and previously described in the population (8,9).

One adverse event that is not widely discussed and has recently emerged is IVIG-induced hemolytic anemia (IH). There are scattered case reports describing this phenomenon, but it has not yet been described in ESRD patients on dialysis (1,10-15). One recent report describes the development of acute kidney injury related to hemoglobinuria as a result of IH (16). In all cases, IVIG was used for a variety of infectious, inflammatory, autoimmune, and hematologic disorders. High cumulative doses were administered, ≥2 g/kg, in most cases. In addition, most patients showed a positive direct antiglobulin test (DAT), and most were of non-O blood type. Various concentrations of anti-A, anti-B, and anti-D hemagglutinins were detected in the different IVIG products that were infused in each case.

We use high-dose IVIG (1 to 2 g/kg) as part of a protocol to desensitize highly HLA-sensitized patients awaiting renal transplant (17). Here, we report on a group of patients that experienced IH while receiving IVIG for desensitization or treatment of AMR. In addition, we examine the IgG titers to A and B blood group antigens in five IVIG products. Renal transplant candidates are under the care of both the renal transplant team and their primary nephrologist while receiving IVIG for desensitization. Furthermore, those with kidney disease may receive IVIG for various other conditions. It is therefore imperative that all providers be aware of this serious complication.

Materials and Methods

From 2003 to 2008, we identified patients who developed anemia (drop in hemoglobin >1 g/dl) after receiving IVIG. The specific IVIG

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product administered was determined by product availability. If possible, patients at risk for hemolysis (non-O blood group) were administered Carimune, a lyophilized preparation with low anti-A/B titers, starting in 2004. Patients scheduled for a living transplant did not receive Carimune regardless of blood type because of the risk of acute kidney injury. All patients were evaluated for hemolysis and other causes of anemia. The incidence of IH was calculated for 2007 and 2008, the years the majority of cases were identified. A *t* test between percents was used to compare the number of cases between the years and among the different IVIG preparations and blood types.

The following laboratory data were collected: DAT, reticulocyte count, lactate dehydrogenase, haptoglobin, total bilirubin, and fractionated bilirubin. The results of any peripheral blood smears were noted. In addition, we recorded demographic information and the date of transplant, if applicable, for each patient. Patient blood type, dates of IVIG infusion, and the specific IVIG products used were also noted. The average drop in hemoglobin was determined by using the closest hemoglobin value before IVIG infusion and the hemoglobin nadir after IVIG infusion. Student *t* test was used to compare the mean decrease in hemoglobin in our patient population to that previously reported in the literature. The number of days between the IVIG dose and the hemoglobin nadir was examined. In addition, we noted whether a blood transfusion was given and, if so, the number of units transfused.

One lot of each of the following IVIG products was obtained and tested *in vitro* for IgG antibodies against A and B blood group antigens: Gammagard liquid (Baxter Pharmaceuticals, Westlake Village, CA), Gamunex (Talecris Biotherapeutics, Research Triangle Park, NC), Carimune (CSL Behring, Bern, Switzerland), Gamimune N (Talecris Biotherapeutics), and Privigen (CSL Behring). Titers were performed at 37°C using anti-human globulin to detect IgG antibodies to blood group antigens A and B.

Results

From 2003 to 2008, 18 cases of IH in 16 different patients were observed (Table 1). All patients received high-dose IVIG, 1 to 2 g/kg. IVIG was administered in three cases for the treatment of AMR and for desensitization in the remaining cases. The average age was 44 yr. There were equal numbers of men and women, representing a racially diverse population. Fourteen of the cases (81%) were blood type A, three cases were type B, and one was type AB. All but two cases were Rh positive (Table 1).

The average drop in hemoglobin was 3.8 g/dl. This was similar to the decrease in hemoglobin reported in the case series by Daw *et al.* ($P = 0.3$) (11). Eighty-three percent of patients required blood transfusions (1 to 4 units) with packed red blood cells to correct symptomatic anemia. The contribution of hemodilution leading to anemia in those receiving IVIG is uncertain; however, all patients received IVIG while on hemodialysis, leading us to believe this contribution is negligible. Hemoglobin nadir was identified anywhere from 1 to 22 d after infusion. A DAT was drawn in 13 cases. They were all positive for IgG and all negative for complement. Ten of 12 patients had an elevated lactate dehydrogenase, whereas 4 of 12 had a low haptoglobin, and 6 of 7 had an elevated reticulocyte count. Total bilirubin was elevated in 3 of 13 cases. A blood smear was done in five cases. They were all normochromic. Three cases displayed oval macrocytes, and two cases had fragmented red blood cells, suggesting hemolysis.

Gamunex was the IVIG product infused in 15 of the cases (Table 1). Privigen was infused in one case and Gammagard liquid in two cases. Antibody titers against A and B blood group antigens from five IVIG products are shown in Figure 1. Isohemagglutinin titers varied among the different products, with Carimune having the lowest titers.

There were a total of 225 IVIG infusions from January 2007 to December 2008, the years when most of the cases were identified. The distribution of IVIG preparations during this time

Table 1. Cases of hemolysis (2003–2008)

Case	Age (yr)	Race	Gender	Blood Type	IVIG Product	Hemoglobin Decrease (g/dl)	DAT	Blood Transfusion (Number of Units)
1	52	H	Female	A+	Gamunex	5.3	IgG+	Yes
2	23	AA	Male	A+	Gamunex	4.7	IgG+	No
3	56	H	Female	A+	Gamunex	5.6	IgG+	Yes (4)
4	27	AA	Female	B+	Gammagard	4.9		Yes (2)
5	36	AA	Male	AB+	Gamunex	5.8	IgG+	Yes (4)
6	37	AS	Female	A+	Gammagard	5.7	IgG+	Yes (2)
7	46	W	Male	A+	Gamunex	3.3		Yes
8	45	H	Female	A+	Gamunex	2.4		Yes
9	66	W	Male	A−	Privigen	3.1		Yes
10	42	W	Female	A+	Gamunex	4.0	IgG+	Yes (2)
11	56	W	Female	A+	Gamunex	3.6	IgG+	No
12	47	W	Female	A−	Gamunex	2.1	IgG+	Yes (2)
13	47	W	Female	A−	Gamunex	2.2		No
14	46	W	Male	A+	Gamunex	2.8	IgG+	Yes (2)
15	73	W	Male	B+	Gamunex	5.3	IgG+	Yes (2)
16	73	W	Male	B+	Gamunex	1.9	IgG+	Yes (2)
17	28	W	Male	A+	Gamunex	2.6	IgG+	Yes (2)
18	21	H	Male	A+	Gamunex	3.0	IgG+	Yes (1)

H, Hispanic; AA, black; AS, Asian; W, white.

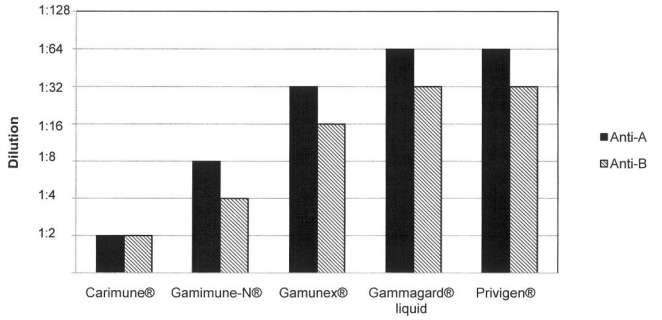

Figure 1. Isohemagglutinin titers in IVIG products. Carimune, the lyophilized product, had the lowest titers. The four liquid preparations tested had higher titers.

period by blood group is detailed in Table 2. Thirteen cases of IH were identified during these years, resulting in an incidence of 5.8%. The incidence in 2008 was greater than in 2007 (8.1% *versus* 3.0%), although this difference was not statistically significant ($P = 0.11$). A subgroup analysis of those at risk for IH (non-O blood type) was also done. The incidence in this group showed a significant increase from 2007 to 2008 ($P = 0.031$). We compared the rate of IH in those that received the low titer, lyophilized preparation Carimune to those that received the higher titer, liquid preparations during these years. There were significantly more cases of IH identified in those that received the liquid IVIG products (Tables 3 and 4). Five cases of IH were identified between January 2003 and December 2006 out of an estimated 289 infusions (incidence, ≈2%).

Discussion

Our group has extensive experience with monitoring the efficacy and safety of IVIG products used in desensitization and for the treatment of AMR (8,9,17). However, our recent experience with newer, isosmolar, liquid products has shown an unexpected risk of IH that was not seen with older products and seems to be related to an increased titer of anti-A/B antibodies in liquid IVIG products. Acute IH has been noted by others in patients treated with IVIG for various hematologic diseases, autoimmune diseases, infections, and neuromuscular disorders. IVIG is crucial to the successful transplantation of highly sensitized renal transplant candidates. It has been used alone or in conjunction with plasmapheresis for desensitization (9,18,19). More recently, IVIG together with rituximab was able to achieve an 80% transplant rate in a population that would otherwise be unlikely to receive a transplant (17).

Table 2. Distribution of IVIG Products 2007–2008

	Gamunex	Carimune	Privigen	Gammagard Liquid
All	139	71	5	10
O	94	15	0	3
A	16	45	5	6
B	29	3	0	1
AB	0	8	0	0

The incidence of IH at our medical center has dramatically increased over the years. There were only five cases identified from 2003 until 2006. The incidence increased in 2007 and 2008 despite our efforts to limit the use of high titer preparations in the population at risk. We believe this trend resulted from the higher index of suspicion of IH. However, our sample size limited the ability to detect a significant increase in incidence in the whole population during these years. In their case analysis, Daw *et al.* (11) estimated the incidence of IH in their population to be 1.6% over a 2.5-yr period, which is significantly less than what is reported here ($P \leq 0.001$). In the NIH IG02 trial, conducted between 1997 and 2000, >300 infusions of IVIG were given to 48 highly sensitized subjects on hemodialysis. There was no hemolysis reported in this closely monitored group. Gamimune N, a liquid IVIG preparation, was used in this trial. Gamimune N had A/B titers <1:16 in our analysis. The lower titers in this product along with the low index of suspicion for hemolysis might be responsible for the results obtained.

Hemolytic anemia after IVIG infusion results from the passive acquisition of A/B isohemagglutinins from the IVIG product. Red blood cells are coated with antibody, and this, in the presence of complement, results in erythrophagocytosis (20,21). Isosmolar, liquid products with higher antibody titers seem more likely to cause hemolysis. We did not identify any hemolysis in those patients that received Carimune, which is lyophilized and found to have low anti-A and anti-B titers. It would therefore seem reasonable to use a product that has lower isohemagglutinin titers in patients at risk for hemolysis. However, this is likely not feasible at all medical centers because of pharmacy purchasing practices. In addition, side effects such as acute renal failure or thrombosis can occur with the higher osmolar products, thereby limiting their use in some situations (8). There has been mixed success preventing hemolytic reactions by removing the antibodies from the IVIG product *in vitro* (20,21). It remains unclear whether removal of antibody will improve outcomes.

Some manufacturers of IVIG have set limits for the concentration of anti-A, anti-B, and anti-D antibodies allowed in their product (5). The European Pharmacopoeia have put forth guidelines that recommend no anti-A or anti-B hemagglutinins be detected at the 1:64 dilution (9). However, there are now many documented cases of IH that occur despite these limits. Anti-A titers >1:16 are more likely to cause clinically significant hemolysis (11,12). Our evaluation of five different IVIG products showed all of the products to be within the guideline, with the exception of the anti-A titers in the lots of Gammagard liquid and Privigen tested. Only one lot of each preparation was tested. It is possible that titers may vary between the lots, and it is unknown if particular lots were associated with IH. The antibody titers were variable between the products, with higher titers seen in the liquid, nonlyophilized products (Figure 1).

Our institution has extensive experience administering various IVIG products to ESRD patients on hemodialysis for desensitization purposes. In this regard, we noted that high osmolar and sucrose-containing products are safe to administer

Table 3. Hemolysis by specific IVIG product and blood type (2007–2008)

	Gamunex (n = 139)	Privigen (n = 5)	Gammagard[a] (n = 10)	Carimune (n = 71)
Total hemolysis	11 (8%)	1 (20%)	1 (10%)	0
Blood type				
A	8 (6%)	1 (20%)	1 (10%)	0
B	3 (2%)	0	0	0
AB	0	0	0	0
No hemolysis	128 (92%)	4 (80%)	9 (90%)	71 (100%)

[a]Gammagard liquid.

with hemodialysis. This is likely because of the removal of the excipient compounds (sodium and sucrose) by the dialyzer and anticoagulation with heparin. Thus, low titer anti-A/B products with high osmolality can be administered to ESRD patients on hemodialysis, which reduces the risk for hemolysis. In 2004, we started using Carimune in all non-O blood types undergoing desensitization. We have subsequently seen no cases of IH in those that received this product to date. Carimune is a lyophilized product and had the lowest titers of the products tested. However, lyophilized products are also hyperosmolar, which limits their use in patients who are either not on dialysis or have residual renal function because of the risk of osmotic nephropathy or thrombotic events.

It has been hypothesized that individuals with an enhanced immunologic state resulting from underlying inflammation may be at increased risk of developing IH (11). All of our cases occurred in patients who were highly sensitized. Therefore, it may be that their enhanced immune reactivity placed them at increased risk of developing hemolysis after IVIG infusions. Furthermore, some individuals with chronic kidney disease have an underlying chronic inflammatory state (22-24). It is possible that chronic inflammation predisposes this group of patients to IH. This chronic inflammatory state may also explain why serum haptoglobin, an acute phase reactant, was not uniformly low in our patient population. Sixty-six percent of the cases had a normal haptoglobin, with the rest having low haptoglobin levels. Similarly, the case series presented by Daw *et al.* (11) reported 60% of their cases having a normal or high haptoglobin, suggesting an underlying inflammatory state. It should be noted that a decrease in haptoglobin was described in two of five healthy volunteers without evidence of hemolysis after receiving IVIG (25).

The avoidance of blood transfusions is important in patients awaiting renal transplant, because alloantibodies may result from this exposure. Blood transfusions were required in 83% of our cases. Daw *et al.* (11) reported only 19% of cases required a blood transfusion. Our mean decrease in hemoglobin of 3.8 g/dl was similar to their reported drop in hemoglobin of 3.2 g/dl (P = 0.3). However, at baseline, our patients were borderline anemic, with a hemoglobin mean of 11.6 g/dl (reference range, 11.6 to 15.4 g/dl), possibly leading to a lower nadir than would otherwise be observed in non-ESRD patients. In addition, there are often other comorbid conditions, such as coronary artery disease, that may lead to a lower threshold for transfusion. The multiple comorbid conditions seen in ESRD patients may also result in increased symptoms from an acute drop in hemoglobin, thereby necessitating a blood transfusion.

The IVIG doses used in the previously reported cases were similar to ours. However, there were multiple cases noted where the cumulative dose was higher. We use a total dose of 2 g/kg given at week 0 and week 4 for desensitization before transplantation (up to a maximum of 140 g for patients >70 kg). The total dose in our series was either given in 1 or 2 d. IVIG was given over multiple days in other reports (1,10-12,15). IH was observed despite dividing the cumulative dose over multiple days. Therefore, it does not seem beneficial to give IVIG over multiple days for the purpose of preventing IH; however, this study was not designed to test this hypothesis.

Preventing and identifying IH can be challenging. It can occur in any blood type, but one should have a higher index of suspicion in non-O blood groups. Some have advocated testing the IVIG product for isohemagglutinin titers before infusion; however, we do not believe this is feasible for all institutions. Alternatively, one may perform a DAT between the recipient's blood and the IVIG product to be infused; however, the predictive value is unknown (1). The use of IVIG with a low isohemagglutinin titer is advisable where possible. We recommend checking a hemoglobin or hematocrit level 48 to 72 h after infusion. If there is a decrease in hemoglobin or hematocrit, one should obtain markers for hemolysis including a DAT. The patient should be monitored for symptoms of anemia and

Table 4. Hemolysis: lyophilized *versus* liquid IVIG (2007–2008)

	Lyophilized[a] (n = 71)	Liquid[b] (n = 154)
Total hemolysis	0	13 (8%)
Blood type		
A	0	10 (6%)
B	0	3 (2%)
AB	0	0
No hemolysis	71 (100%)	131 (92%)

[a]Carimune.
[b]Gamunex, Gammagard liquid, and Privigen.

the blood count followed if a hemolytic reaction becomes apparent. Transfusion of packed red blood cells should be avoided if at all possible in this patient population to prevent further allosensitization. If a blood transfusion is necessary, leukocyte-reduced blood products are preferred. Further studies are needed to determine whether removing isohemagglutinins from IVIG products is a feasible and effective strategy for reducing IH. Other potential solutions would be slower infusion of immune globulin through alternate sites (*i.e.,* subcutaneous IVIG infusions) because this may allow for absorbance of anti-A/B titers in the immune globulin products before it accesses the red blood cells. Currently, this is not proven, but should be studied as a method to prevent IH.

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Disclosures

None.

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