Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following $Rh_o(D)$ immune globulin intravenous administration for immune thrombocytopenic purpura

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The Food and Drug Administration (FDA) licensed $Rh_o(D)$ immune globulin intravenous (anti-D IGIV) on March 24, 1995, for treatment of immune thrombocytopenic purpura (ITP). A previous review described data on 15 patients who experienced acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP or secondary thrombocytopenia. Eleven of those patients also experienced clinically compromising anemia, transfusion with packed red blood cells, renal insufficiency, dialysis, or death. That review suggested that patients receiving anti-D IGIV be monitored for those and other potential complications of hemoglobinemia, particularly disseminated intravascular coagulation (DIC). Through November 30, 2004, the FDA received 6 reports of DIC associated with "acute hemolysis" (or similar terms), 5 of which involved fatalities. The attending or consulting physicians assessed that acute hemolysis or DIC caused or contributed to each death. This review presents the first case series of DIC associated with acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP. The purpose of this review is to increase awareness among physicians and other health care professionals that DIC may be a rare but potentially severe complication of anti-D IGIV treatment. Increased awareness of DIC as a diagnostic possibility may enable prompt recognition and medical intervention in affected patients. (Blood. 2005; 106:1532-1537)

Introduction

The Food and Drug Administration (FDA) licensed $Rh_o(D)$ immune globulin intravenous (anti-D IGIV; then WinRho, currently WinRho SDF, Cangene Corporation, Winnipeg, MB, Canada) on March 24, 1995, for treatment of immune thrombocytopenic purpura (ITP) in $Rh_o(D)$-positive, nonsplenectomized children with acute ITP, children and adults with chronic ITP, and children and adults with ITP secondary to HIV infection. It is currently the only anti-D IGIV licensed for this indication in the United States. The FDA also approved anti-D IGIV for suppression of Rh isoimmunization, and it is used for treatment of "off-label" thrombocytopenias (eg, secondary thrombocytopenia) to an unknown extent.

The presumed mechanism of action of anti-D IGIV in ITP involves extravascular hemolysis of anti-D–sensitized red blood cells (RBCs) by splenic macrophages, which results in decreased splenic sequestration of autoantibody-sensitized platelets and an increased platelet count.[1] Although seemingly inconsistent with this mechanism of action, 2 cases involving "acute-onset hemoglobinuria consistent with intravascular hemolysis" were noted in the anti-D IGIV clinical trials for ITP.[2]

Following licensure, additional cases of acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP or other thrombocytopenias were submitted to the FDA and were previously reported.[3] That review described data on 15 patients, 11 of whom experienced additional complications: 7 developed sufficient decreases in hemoglobin levels to prompt orders for transfusions of packed red blood cell (PRBCs), although only 6 underwent transfusion; 8 experienced onset or exacerbation of renal insufficiency, 2 of whom underwent dialysis; 1 died from pulmonary edema and respiratory distress secondary to exacerbated anemia; and 6 experienced 2 or 3 of these complications concurrently. That review suggested that patients receiving anti-D IGIV for ITP or secondary thrombocytopenia be closely monitored for signs and symptoms of those or other potential complications of hemoglobinemia, notably disseminated intravascular coagulation (DIC). Although additional case reports of "acute hemolysis" (or similar terms) following anti-D IGIV administration were subsequently published,[4-10] no hemolysis-associated complications beyond those described in the 15-patient case series were reported.

This review presents the first case series of DIC associated with acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP and is based on continued postmarketing surveillance of adverse event reports submitted to the FDA. The case series consists of 6 patients: 1 child, who recovered without sequelae, and 5 adults, all of whom died. Attending or consulting physicians assessed that acute hemolysis or DIC caused or contributed to each death.

Patients and methods

Case series patients

Anti-D IGIV adverse event reports submitted to the FDA between the March 24, 1995, licensure of anti-D IGIV and November 30, 2004, were

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reviewed. Available data for these cases consisted of the information in the initial reports and supplemental clinical and laboratory information (eg, patient medical records) that was obtained through telephone or written follow-up with attending and consulting physicians and other health care professionals.

Case series definition for acute hemoglobinemia or hemoglobinuria

A report met the case definition if it involved acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP. As in the previous 15-patient case series, "acute" was defined as within 4 hours of anti-D IGIV administration; "hemoglobinemia" was defined as an increased serum hemoglobin level or an anecdotal report of "visibly red serum" (or similar terms); "hemoglobinuria" was defined as a positive urine reagent strip test for blood and a urinary sediment with fewer RBCs than would correspond to the degree of positivity of the reagent strip or an anecdotal report of "tea-colored urine" (or similar terms).

Case series definition for DIC

A report met the case definition if it involved DIC associated with acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP. DIC was defined in terms of laboratory or histologic criteria.[11-15] The laboratory criterion was an increased serum fibrin degradation/fibrin split products (FDP/FSP) test result or an increased plasma d-dimer test result. (Because all patients were thrombocytopenic prior to anti-D IGIV administration, a decreased platelet count was not included as a laboratory criterion even though it is considered a diagnostic hallmark of DIC.) Histologic criteria were the presence of microthrombi at autopsy and an assessment by the pathologist that these findings were consistent with a diagnosis of DIC.

Reporting rate for DIC secondary to acute hemoglobinemia or hemoglobinuria

The actual incidence rate (eg, occurrences per 100 000 patients[16]) of DIC associated with acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP or other thrombocytopenias is unknown. Therefore, an estimated reporting rate (eg, adverse event reports per 1 000 000 prescriptions[16]) was calculated to provide a frame of reference. The numerator was the number of credible US cases in the FDA adverse event database that were received during the time period of this review. The denominator was derived from sales data obtained by the FDA from IMS Health (Fairfield, CT). The source of the data was the IMS Health, IMS National Sales Perspectives, which is a continuing monthly report that measures projected dollars and units of pharmaceutical product purchases in all distribution channels in the United States. The data were from the Non-Retail Channels of Distribution, Calendar Year 1995-1998, Calendar Year 1999-2003, and Year to Date January-November 2004, and consisted of the units of anti-D IGIV distributed in nonretail markets (eg, nonfederal hospitals, federal facilities, clinics, health maintenance organizations, home health care agencies).[17-19]

Results

Pretreatment and posttreatment profile of case series patients

The FDA received these 6 reports between May 21, 1999, and October 12, 2004 (Table 1). None of the patients had physicians or health care facilities in common. All cases occurred within the United States and were distributed across 6 states.

Four patients met the acute criterion of the hemoglobinemia or hemoglobinuria case definition (Table 1). For the other 2 patients, information was unavailable to assess whether the time of onset of signs and symptoms following administration of anti-D IGIV met this criterion (Table 1). All 6 patients met the criteria for hemoglobinemia or hemoglobinuria (Table 1).

All 6 patients met the criteria for the DIC case definition (Table 2). In addition to the case definition criteria, other related laboratory criteria (eg, prothrombin [PT] and partial thromboplastin time [PTT] test results), if and when available, were also noted (Table 2).

All patients received anti-D IGIV for treatment of ITP (Table 1). Five patients received the recommended 50-μg/kg anti-D IGIV dose; 1 patient received 75 μg/kg (Table 1). The anti-D IGIV lot numbers administered were available for only 2 patients. The FDA's adverse event database had no other reports for those lots that suggested hemoglobinemia or hemoglobinuria and DIC. Only one patient had previously received anti-D IGIV.

One patient was a child (boy, aged 12 years); the other 5 patients were adults (ages 25, 67, 71, 75, 85 years; 3 men, 2 women; Table 1). All patients were clinically stable and were initially discharged home following anti-D IGIV administration. They all subsequently sought medical attention and were hospitalized for signs and symptoms that followed anti-D IGIV administration.

The mean decrease between the pretreatment hemoglobin level and the nadir posttreatment hemoglobin level prior to hospital discharge or death was 5.8 g/dL (range, 3.0-9.6 g/dL; Table 3). However, 4 patients received multiple transfusions of PRBCs during the course of their hospitalizations (Table 3); their hemoglobin level decreases might have been of greater magnitude if not offset by transfusion. Four patients whose baseline serum creatinine levels were within normal limits developed renal insufficiency; 2 of those patients underwent dialysis (Table 3). The pediatric patient was subsequently discharged from the hospital in

Table 1. Case characteristics, definition, and related criteria for acute hemoglobinemia or hemoglobinuria

Case no.	Age, y	Sex	FDA received initial report	Indication for anti-D IGIV	Dose, μg/kg	Acute hemoglobinemia or hemoglobinuria case definition (and related) criteria			
						Acute*	Hemoglobinemia†	Hemoglobinuria‡	MD assessment§
1	12	M	May 1999	ITP	50	—‖	—¶	Yes	Yes
2	85	M	Aug 1999	ITP	50	Yes	Yes	Yes	Yes
3	75	M	Aug 2002	ITP	48	Yes	—¶	Yes	Yes
4	25	F	Sep 2003	ITP	50	—‖	—¶	Yes	Yes
5	71	F	Sep 2004	ITP	75	Yes	—¶	Yes	Yes
6	67	M	Oct 2004	ITP	51	Yes	—¶	Yes	Yes

— indicates no information available.

*Signs or symptoms within 4 hours of anti-D IGIV administration.

†Increased serum hemoglobin level or anecdotal report of "visibly red serum" (or similar terms).

‡Positive urine reagent strip test for blood and urinary sediment with fewer RBCs than would correspond to degree of positivity of reagent strip or anecdotal report of "tea-colored urine" (or similar terms).

§Attending or consulting physician assessment that hemoglobinemia or hemoglobinuria occurred.

‖Exact time of onset indeterminate due to incomplete medical history.

¶Relevant laboratory test results not available or not optimally timed.

Table 2. Case definition and related criteria for DIC

Case no.	Increased PT	Increased PTT	Decreased fibrinogen level	Increased FDP/FSP	Increased d-dimer	Autopsy consistent with DIC*	MD assessment†
1	Yes	Yes	Yes	Yes	Yes	—‡	Yes
2	—§	—§	—§	—§	Yes	Yes	Yes
3	—#	—#	—#	Yes	Yes	—‖	Yes
4	—§	—§	—§	—§	Yes	Yes	Yes
5	Yes	Yes	—§	Yes	Yes	—¶	Yes
6	Yes	—§	—§	—§	Yes	—‖	Yes

— indicates no information available.
*Findings positive for microthrombi and assessed by pathologist as consistent with DIC.
†Attending or consulting physician assessment that DIC occurred.
‡Not applicable because patient recovered.
§Relevant laboratory test results not available or not optimally timed.
‖Although patient died, autopsy not performed.
¶Although patient died and autopsy performed, no findings relevant to DIC noted.
#Laboratory test results within normal limits.

stable condition without sequelae, but all 5 adult patients remained hospitalized and died between 3 and 10 days after anti-D IGIV administration (Table 3).

The clinical assessment of the attending or consulting physicians was that each patient experienced both acute hemolysis and DIC (Tables 1-2). None of the physicians could identify an alternative to hemoglobinemia as the precipitating event for the DIC. They further assessed that acute hemolysis or DIC caused or contributed to each death.

The time of onset of signs and symptoms and the clinical presentation, course, and outcome of the 6 patients varied considerably.

Case 1. This 12-year-old boy presented 5 days after receiving anti-D IGIV when his dizziness and weakness prompted medical evaluation. Physical examination revealed numerous ecchymoses, petechiae, and hemorrhages. He reported voiding "tea-colored" urine following anti-D IGIV administration but denied fever, vomiting, diarrhea, or other notable signs or symptoms at that time. He was hospitalized for what was subsequently diagnosed as ITP- and DIC-related bleeding complications. His hemoglobin level later that day was 4.4 g/dL, which was decreased from a pretreatment baseline of 14.0 g/dL. Over the next several days, he received multiple transfusions of PRBCs, platelets, and fresh-frozen plasma for persistent hemorrhages. Blood cultures were negative. When treatment with steroids, vincristine, intravenous immune globulin, and plasmapheresis failed to increase his platelet count, he underwent an uneventful splenectomy and was discharged 18 days after admission in stable condition without sequelae.

Case 2. An 85-year-old man was observed for 45 minutes following anti-D IGIV administration and released. En route home, he developed back and leg pain, chills, fever, chest tightness, and clamminess. The chest tightness and clamminess persisted for approximately 1.5 hours; the back and leg pain persisted and worsened overnight. He presented the next day with increasing dyspnea and possible atrial fibrillation. He was admitted with a presumptive diagnosis of an acute hemolytic reaction to the anti-D IGIV and to rule out myocardial infarction. Myocardial infarction was subsequently ruled out. He developed laboratory evidence of both renal insufficiency and DIC, which were presumed to be secondary to the hemolysis. Sepsis was considered but was subsequently ruled out as a confounding complication. He was intubated for worsening respiratory distress and hypoxia, which were attributed to possible pulmonary microemboli and noncardiogenic pulmonary edema. He progressed to multiorgan failure and died 3 days following anti-D IGIV administration. Autopsy findings included "[diffuse involvement of the lungs] with small platelet thrombi consistent with [his] clinical diagnosis of DIC," renal histology showing "features of acute tubular necrosis," and DIC listed as related to or contributing to his death.

Case 3. A 75-year-old man presented within 2 hours of anti-D IGIV administration with complaints of feeling cold and clammy and severe low back pain radiating toward the knees. Following admission, he developed chest pain and was diagnosed with acute non–Q-wave myocardial infarction. Further evaluation ruled out a pulmonary embolus as the cause of his developing acute respiratory distress syndrome (ARDS). He subsequently developed laboratory evidence of DIC and renal insufficiency. Both ARDS and DIC were attributed to anti-D-IGIV–induced hemolysis. He was designated "do not resuscitate" and died 4 days following anti-D IGIV administration, with the cause of death

Table 3. Hemoglobin levels and adverse events reported after treatment with anti-D IGIV

	Hemoglobin level, g/dL		Adverse events experienced after treatment						
Case no.	Before treatment	After treatment	Decrease in hemoglobin level, g/dL	Hemoglobinemia* or hemoglobinuria†	Renal insufficiency	Dialysis	PRBCs, U‡	DIC	Death, d§
1	14.0	4.4	9.6	Yes	—	—	≥ 5‖	Yes	—
2	13.2	10.0	3.2	Yes	Yes	—	—	Yes	3
3	11.0	8.0	3.0	Yes	Yes	—	—	Yes	4
4	11.1	3.0	8.1	Yes	—	—	> 2‖	Yes	10
5	11.1	6.9	4.2	Yes	Yes	Yes	2	Yes	3
6	13.9	7.3	6.6	Yes	Yes	Yes	2	Yes	3

— indicates no information available.
*Increased serum hemoglobin level or anecdotal report of "visibly red serum" (or similar terms).
†Positive urine reagent strip test for blood and urinary sediment with fewer RBCs than would correspond to degree of positivity of reagent strip or anecdotal report of "tea-colored urine" (or similar terms).
‡Number of units of packed red blood cells transfused.
§Number of days after treatment that patient died.
‖Available patient medical records incompletely documented.

listed as ARDS and myocardial infarction. No autopsy was performed.

Case 4. A 25-year-old woman presented with chest pain 8 days after receiving anti-D IGIV. She reported having "not felt well" for "several days" but had not sought medical attention due to a lack of health insurance. At that time, in addition to a decrease of 5.6 g/dL from her pretreatment hemoglobin level of 11.1 g/dL, she had laboratory evidence of both hemoglobinuria and DIC. Pulmonary embolism was ruled out, as was overt bleeding from gastrointestinal and other sources. She received PRBCs before being discharged home. Despite still "not feeling well," recurrent chest pain, shortness of breath, nausea, vomiting, and vertigo, she again delayed seeking follow-up medical attention for another 2 days. Following admission, transfusions with PRBCs were discontinued "since [they] seem[ed] to result in more hemolysis." She continued to deteriorate, despite treatment with steroids and intravenous immune globulin to reduce the hemolysis, dopamine for hypotension, and intubation for severe respiratory distress. At the time of her death 10 days after anti-D IGIV administration, her hemoglobin level was 3.0 g/dL, and her urine remained positive for hemoglobinuria. Autopsy findings included myocarditis, possibly due to a viral infection or brought on by the hemolytic episode, and microthrombi in cardiac, coronary artery, and kidney sections, deemed consistent with DIC. She had received anti-D IGIV 5 months earlier without apparent complication.

Case 5. A 71-year-old woman experienced acute dyspnea and "exquisite back pain" within 10 minutes of anti-D IGIV administration. Following the onset of chills, rigors, sweating, hypotension, hypoxia, and tachycardia, she was admitted with a presumptive diagnosis of "hemolytic transfusion reaction." She developed acute renal failure, for which she underwent dialysis, increased respiratory distress, and laboratory evidence of DIC. She experienced increasing confusion, disorientation, hypertension, dyspnea, and tachycardia. Blood cultures remained negative. She had been designated "do not resuscitate" and died 3 days after anti-D IGIV administration. The treating physician cited renal failure secondary to hypotension secondary to an "acute drug reaction" as the presumed cause of death. Autopsy revealed no evidence of hemorrhage, pulmonary embolus, myocardial infarction, cerebrovascular accident, or DIC. Her death was attributed to her primary underlying condition of chronic lymphocytic leukemia as well as disseminated cytomegalovirus infection, which was evident on autopsy. However, hemoglobinemia or DIC was cited by the attending physician as having exacerbated her condition and contributed to her death.

Case 6. This case involved a 67-year-old man who experienced diffuse paresthesias, chest discomfort, and general restlessness within 20 minutes of anti-D IGIV administration, followed by back pain and leg cramping. After admission, he was asymptomatic overnight. The next day, however, he appeared severely jaundiced, became diaphoretic, experienced dyspnea, and became hypotensive. His hemoglobin level had decreased 6.6 g/dL from 13.9 g/dL at baseline, and laboratory evidence indicated both renal failure and DIC. He underwent dialysis, received multiple platelet and PRBC transfusions, and was treated for ventricular fibrillation. Although he stabilized and his attending physician was optimistic about his recovery, his family refused further medical intervention. The patient died 3 days following anti-D IGIV administration. His death was attributed to cardiac and renal failures, intravascular hemolysis, and his underlying myelodysplastic syndrome. No autopsy was performed.

Reporting rate for DIC associated with acute hemoglobinemia or hemoglobinuria

In calculating the estimated reporting rate, the numerator was 6, which was the number of US cases included in this case series. The denominator of 121 389 was the estimated number of anti-D IGIV infusions administered in the United States for ITP or other thrombocytopenias during the time period for this review. The resulting reporting rate for DIC associated with acute hemoglobinemia or hemoglobinuria was 0.005% of anti-D IGIV infusions, when expressed as a percentage, or 1 case/20 232 anti-D IGIV infusions, when expressed as a ratio.

Discussion

Case series

The case definitions for this review represented a compromise, balancing the criteria from standard definitions against the variable clinical and laboratory data that were available for each patient (Tables 1-3). Data on some reports remained incomplete, despite follow-up inquiries to physicians and other health care professionals and for various reasons (eg, a laboratory test was not ordered, only a partial medical record was available). Relevant pretreatment data were generally unavailable to rule out preexisting hemolysis or DIC. Despite these limitations, the case definitions identified reports that appeared to be credible cases of DIC associated with acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP.

Reporting rate for DIC secondary to acute hemoglobinemia or hemoglobinuria

The calculated reporting rate should not be interpreted as an incidence rate due to important limitations for both the numerator and the denominator.[16] The FDA data likely underestimate the number of cases of DIC associated with acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP or other thrombocytopenias. Underreporting is pervasive in passive surveillance programs like FDA's MedWatch adverse event reporting system[16,22-26] and is attributable to various factors (eg, the reliance on voluntary reporting, the length of time a product has been on the market, the seriousness of the adverse event).[16,22-27] Although not examined specifically for MedWatch, the percentage of serious adverse events reported to other passive surveillance systems has been estimated to include only 1% to 38% of those that occur.[22,24-26]

Furthermore, when adjusted for US market distribution, the overall reporting rate for serious anti-D IGIV adverse events submitted to the FDA, which peaked approximately 2 years after licensure, has progressively decreased since then, despite of increased postlicensure market distribution of anti-D IGIV.[17-19] This phenomenon, termed the Weber effect, has been observed with other prescription products once the initial product "newness" has waned.[24-27] Because the degree of underreporting to MedWatch for anti-D IGIV is unknown, however, no "correction" factor was applied to the anti-D IGIV reporting rate.

The IMS Health data may underestimate or overestimate the units of anti-D IGIV distributed because the data are based on a limited sample of US health care facilities.[17-19] Conversion of the IMS Health data from units distributed to an estimated number of infusions required certain broad assumptions (eg, the mean μg/kg dose administered, the percentage of anti-D IGIV infusions for

suppression of Rh isoimmunization). Although referenced to the pharmacovigilance and anti-D IGIV literature to the extent possible,[3,16,28,29] these and other assumptions used in calculating the reporting rate may not reflect actual clinical usage in the United States. Despite these limitations, the reporting rate suggests that DIC associated with acute hemoglobinemia or hemoglobinuria following anti-D IGIV administration for ITP is at most a rare event.

Five additional reports that were submitted to the FDA during the time period for this review suggested both acute hemolysis and DIC. These cases were not included in this case series, however, because they lacked sufficient laboratory data to corroborate that both acute hemolysis and DIC occurred. It is likely that there were other cases of hemolysis-associated DIC that were not reported to either the FDA or the anti-D IGIV manufacturer.

Mechanism of DIC

Following transfusion[11-15,30] and in other clinical situations,[13,15,31] DIC secondary to hemoglobinemia is recognized as a potential complication and is presumed to result from activation of the coagulation system by complement-fixing immune complexes or cytokine-released tissue factor or both. Based on temporal relationships and biologic plausibility, the DIC in these 6 cases may have been causally related to hemoglobinemia. Evidence for a causal relationship between DIC and acute hemolysis following anti-D IGIV administration is strengthened by the lack of alternatives to hemoglobinemia as the precipitating event for DIC. However, a causal relationship between hemoglobinemia and DIC in these patients cannot be confirmed or ruled out on the basis of the clinical and laboratory information available. Other primary causes (eg, undetected sepsis) or comorbid conditions (eg, malignancy) could have independently initiated DIC.[11-15]

The signs and symptoms of DIC that were experienced by the case series patients appeared consistent with that diagnosis. However, it can be difficult to diagnose DIC according to a classical definition because of considerable variation in the clinical and laboratory findings of DIC. The clinical presentation can vary in time of onset and in degrees of hemorrhage or thrombosis. The clinical course and outcome can range from complete recovery without sequelae to multiorgan dysfunction and severe morbidity and mortality. There can likewise be variation in the extent to which clinical manifestations and severity are directly correlated with laboratory (and autopsy) findings.[11-15] The case series patients likewise reflected considerable diversity. Furthermore, laboratory diagnosis of DIC generally includes a relatively standard panel of tests.[11-15] However, the only test result that was available for all case series patients was d-dimer. Among other tests usually ordered, FDP/FSP results were available for only 3 patients; both PT and PTT results were available for only 3 patients, and fibrinogen levels were available for only 2 patients (Table 2).

Mechanism of acute hemoglobinemia or hemoglobinuria

The time of onset, signs and symptoms, and potential complications of acute hemolysis that were experienced by the previous 15 and these 6 additional patients were consistent with the variable presentations of intravascular hemolysis in acute hemolytic transfusion reactions[11-15], ranging from asymptomatic hemoglobinuria to severe DIC-induced sequelae. The presumed mechanism of action of anti-D IGIV, which involves immune-mediated hemolysis, and the temporal association between anti-D IGIV administration and the onset of hemoglobinemia or hemoglobinuria suggests a causal relationship. However, the etiology of the hemoglobinemia or hemoglobinuria in these patients has not yet been established as "intravascular hemolysis" in terms of immune-mediated or other mechanisms of hemolysis.[3,6,7,10,20,21] Additionally, the laboratory test results generally available for these patients were routine urinalysis results that were consistent with hemoglobinuria and were presumed to represent hemoglobinuria, given the context of acute hemolysis. However, myoglobinuria, which is also consistent with these results, was not ruled out in all patients. For these reasons, this review continues to refer to "acute hemoglobinemia or hemoglobinuria" instead of more succinct terms (eg, "intravascular hemolysis").

According to the professional package insert, anti-D IGIV contains high-titered anti-D and low-titered anti-A, anti-B, anti-C, and anti-E blood group antibodies,[1,32] all of which can be passively acquired.[1,32,33] Prior to release of lots for market distribution, the manufacturer quantitatively assays these blood group antibodies to ensure compliance with FDA specifications. However, it has been reported that anti-D IGIV may, in addition, contain other low-titered blood group antibodies (eg, anti-Duffy^a [anti-Fy^a], anti-Kidd^a [anti-Jk^a]).[33] These other blood group antibodies can likewise be passively acquired, show lot-to-lot variability in identities and titers,[33] and are neither qualitatively nor quantitatively assayed during manufacture or prior to lot release for market distribution.

Could the collective array of passively acquired blood group antibodies in anti-D IGIV sensitize a critical mass of RBCs (in correspondingly antigen-positive patients) and result in immune-mediated complement activation and intravascular hemolysis? Although thought unlikely except with passive transfer of a significant volume of high-titered blood group antibodies,[30] this hypothesis warrants further consideration. Patients who experience acute hemoglobinemia or hemoglobinuria following receipt of anti-D IGIV for ITP or other thrombocytopenias might provide the most relevant opportunity for further investigation of this hypothesis. Of particular interest would be the patient RBC antigen phenotype, the identities and titers of the blood group antibodies in the anti-D IGIV lots administered, and hemolysis–end-point compatibility testing of patient RBCs and the anti-D IGIV lots administered.

Previous, uneventful administration of anti-D IGIV provides no assurance that a subsequent administration will be uneventful. This assertion is based on 4 patients: 1 patient from the current case series, 2 patients from the previous case series, and 1 patient from a foreign case report in the literature.[10] The 3 case series patients each received anti-D IGIV without complication on one previous occasion and experienced acute hemoglobinemia or hemoglobinuria after a subsequent anti-D IGIV administration (ie, 5 months, 6 months, 1 week later). Two of those patients died following the second infusion; the other patient survived but was not retreated with anti-D IGIV. The patient in the literature report was treated for ITP without incident every 10 to 20 days for 8 years with either 5.5 or 4.0 μg/kg of an unspecified trade name of anti-D IGIV. She subsequently and unexpectedly experienced "hemolysis/hemoglobinuria" but no sequelae on each subsequent administration of anti-D IGIV over the next 6 months.

The anti-D IGIV lot-to-lot variability of other blood group antibody identities and titers might account for the observation that previous uneventful administration of anti-D IGIV may be associated with acute hemoglobinemia or hemoglobinuria after a subsequent infusion. This hypothesis likewise warrants further consideration. It could similarly be evaluated by determining the RBC antigen phenotype of the affected patient, by determining the blood

group antibody identities and titers in the anti-D IGIV lots administered uneventfully and those associated with acute hemolysis, and by performing hemolysis–end-point compatibility testing with patient RBCs and the anti-D IGIV lots administered without incident and those associated with acute hemoglobinemia or hemoglobinuria.

Summary

This review reinforces the suggestion that patients should be closely monitored for signs and symptoms of acute hemoglobinemia or hemoglobinuria, clinically compromising anemia, and renal insufficiency following anti-D IGIV administration for ITP or other thrombocytopenias.[1,3,32,34] It further suggests that it may be prudent to monitor patients experiencing those events for signs and symptoms of DIC. It should also be noted that previous uneventful administration of anti-D IGIV does not preclude the occurrence of acute hemoglobinemia or hemoglobinuria following subsequent administration of anti-D IGIV.

Physicians and other health care professionals are encouraged to submit serious adverse event reports for anti-D IGIV or any FDA-approved product directly to FDA or to the product manufacturer.[3,6,22,23,32,34] Adverse events may be reported to FDA's adverse event reporting system, MedWatch, by Internet at http://www.fda.gov/medwatch; by telephone at 1-800-FDA-1088; by fax at 1-800-FDA-0178; or by mail at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Information about the MedWatch program, instructions and forms for submitting adverse event reports to the FDA, and safety alerts about FDA-approved products are available at the MedWatch Web site. Contact information for reporting adverse events to the anti-D IGIV manufacturer[1,35] or to other product manufacturers is generally available in professional package inserts or on manufacturer- or distributor-sponsored Web sites.

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