Acute onset hemoglobinemia and/or hemoglobinuria and sequelae following Rh\(_{0}(D)\) immune globulin intravenous administration in immune thrombocytopenic purpura patients

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\(\text{Rh}_{0}(D)\) immune globulin intravenous (anti-D IGIV) was licensed by the United States Food and Drug Administration (FDA) in March 1995 to treat patients with immune thrombocytopenic purpura (ITP).

Anti-D IGIV induces extravascular hemolysis, an expected adverse reaction that is consistent with the presumed mechanism of action. Between licensure and April 1999, the FDA received 15 reports of hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration that met the case definition for this review. The mechanism responsible for hemoglobinemia and/or hemoglobinuria is unexplained. Review of these reports was prompted by the seriousness and the unexpectedness of treatment-associated sequelae experienced by 11 patients. Of these patients, 7 developed sufficient onset or exacerbation of anemia that orders were written for packed red blood cell transfusions, although only 6 patients were transfused. Eight patients experienced the onset or exacerbation of renal insufficiency, and 2 patients underwent dialysis. One patient died due to complications of exacerbated anemia. Six patients experienced 2 to 3 sequelae. Absent validated incidence data, a 1.5% estimated incidence rate from published clinical trial data and a 0.1% estimated reporting rate from FDA and drug utilization data were calculated for reported cases of hemoglobinemia and/or hemoglobinuria. This review presents the first case series of anti-D-IGIV–associated hemoglobinemia and/or hemoglobinuria and provides pretreatment and posttreatment clinical and laboratory findings of the case series patients. The primary purpose of this review is to increase awareness of this potentially serious occurrence among physicians and health care professionals who manage ITP patients treated with anti-D IGIV, thereby enabling prompt recognition and treatment of sequelae. (Blood. 2000;95:2523-2529)

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**Introduction**

\(\text{Rh}_{0}(D)\) immune globulin intravenous (anti-D IGIV) was licensed by the United States Food and Drug Administration (FDA) in March 1995 for the treatment of immune thrombocytopenic purpura (ITP) in D-positive, non-splenectomized children with acute ITP, children and adults with chronic ITP, and children and adults with ITP secondary to human immunodeficiency virus (HIV) infection.\(^1\) The primary mechanism of action of anti-D IGIV in ITP patients is presumed to involve the Fc blockade. This mechanism involves competitive binding of anti-D–sensitized red blood cells (RBCs) to macrophage Fc receptors within the spleen, thereby reducing the extent of sequestration and destruction of the patient’s antibody-sensitized platelets.\(^1,2\)

For the management of ITP, the recommended initial dose of anti-D IGIV is 50 µg/kg via intravenous administration over 3 to 5 minutes for patients with a hemoglobin level of at least 100 g/L.\(^1\) For patients with a hemoglobin level of less than 100 g/L, the recommended initial dose is reduced to 25 to 40 µg/kg to lessen the likelihood of significantly exacerbating preexisting anemia, particularly in patients with a hemoglobin level of less than 80 g/L.\(^1\) In patients who respond therapeutically to anti-D IGIV, an increased platelet count is observed, generally beginning within 1 to 3 days, peaking within 7 to 14 days, and persisting for approximately 30 days.\(^1,2,4,6,11,13\) The dose and frequency of any subsequent treatment is dependent upon the patient’s clinical response to the initial dose, in conjunction with other considerations.\(^1,2,4,7\)

The anti-D contained in a 300-µg vial of anti-D IGIV effects the sensitization and sequestration of approximately 17 mL of D-positive RBCs,\(^1\) which are presumed to be destroyed primarily via extravascular hemolysis.\(^1,7\) Thus, a decrease in hemoglobin is a known therapeutic consequence\(^1,2,4,6,10,14\) and is listed in the package insert as an expected adverse event.\(^1\) A decrease in hemoglobin may be initially noted within hours of anti-D IGIV administration,\(^2,7\) with a maximum decrease generally observed within 1-2 weeks.\(^1,2,4,6,8,11,13\) Among 137 ITP patients treated with anti-D IGIV in the clinical trial, the mean hemoglobin decrease was 17 g/dL (range: 4 to 61 g/dL), with decreases of more than 40 g/dL (range: 42 to 61 g/dL) observed in only 3.7% of those patients.\(^1,6\)

Anti-D IGIV is produced by stimulating human plasma donors with D-positive RBCs\(^1,15,16\) and is manufactured from pools of donor plasma to contain more than 90% polyclonal immunoglobulin G (IgG) anti-D.\(^1,6,15,17,18\) Concentrations of IgG, IgG, and IgG are comparable to those of normal serum, and concentrations of IgG are negligible.\(^17\) Anti-D IGIV contains low-titered anti-A, anti-B, anti-C, and anti-E blood group antibodies\(^1,17,18\) that may be passively acquired and may be detectable in posttreatment direct antiglobulin tests (DAT) and indirect antiglobulin tests (IAT).\(^1\)
Pharmacokinetic studies indicate that peak levels of anti-D are achieved within 2 hours of administration of anti-D IGIV and that the in vivo half-life of anti-D is approximately 24 days.\(^1\) Lyophilized anti-D IGIV is stable when stored at 2 to 8°C, and reconstituted anti-D IGIV is stable when stored at room temperature for 12 hours.\(^{1,17}\)

In April 1998 the manufacturer of anti-D IGIV revised the package insert to note “rare reports of acute onset hemoglobinuria consistent with intravascular hemolysis,” following 5 postmarketing surveillance reports of hemoglobinuria in association with anti-D IGIV treatment of ITP patients.\(^1\) There were 2 other revisions at that time stating that hemoglobinuria was “possibly accompanied by reversible acute renal impairment” and that “[s]ome cases [of hemoglobinuria] occurred in patients receiving red blood cell transfusion concurrently with [anti-D IGIV].”\(^1\)

This case series evolved from FDA postmarketing surveillance of adverse event reports involving possible hemoglobinemia and/or hemoglobinuria following administration of anti-D IGIV for the ITP indication. Evaluation of these reports and the subsequent case series development were prompted primarily by the seriousness and unpredictedness of the sequelae reported. As defined by the FDA, “serious” includes medical intervention and initial or prolonged hospitalization, among other criteria, and “unexpected” refers to adverse events not listed in the package insert. Furthermore, the hemoglobinemia and/or hemoglobinuria was unexpected, on the basis of the then-current package insert, and unexplained by the case series data. The impetus for this case series review was the FDA’s follow-up investigation of these reports and a review of the literature. Both the follow-up and the literature suggested that physicians and health care professionals who manage ITP patients treated with anti-D IGIV might be relatively unaware of what appears to be an uncommon but a potentially serious complication.

**Patients and methods**

**Case series definition**

A case was considered evaluable and was included in the case series if it involved the acute onset of hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration for the ITP indication. Acute onset corresponded to less than or equal to 4 hours following anti-D IGIV administration. Hemoglobinemia was defined as either an increased plasma hemoglobin or an anecdotal report of “visibly red serum.” Hemoglobinuria was defined as routine urinalysis results of a positive reagent strip test for blood and a urinary sediment examination revealing fewer RBCs than would be expected on the basis of the positive reagent strip test.\(^{19}\) Positive reagent strip results were presumed to represent hemoglobinuria, given the context of hemolysis of anti-D–sensitized RBCs, although myoglobinuria was not ruled out in all patients.

Sequelae were serious, unexpected adverse events, as defined by the FDA and based on the March 1995 and April 1998 package inserts, that occurred in association with hemoglobinemia and/or hemoglobinuria. Based on those criteria, sequelae included orders written for transfusion with packed RBCs (PRBCs), onset or exacerbation of renal insufficiency, renal dialysis, and death.

**Frequency estimates of hemoglobinemia and/or hemoglobinuria associated with anti-D IGIV administration for the ITP indication**

The actual incidence of hemoglobinemia and/or hemoglobinuria associated with anti-D IGIV administered for the ITP indication is unknown. In the absence of validated incidence data, frequency estimates for incidence rate and incidence were calculated. The incidence rate was defined as the percentage of the US population of ITP patients treated with anti-D IGIV who experienced hemoglobinemia and/or hemoglobinuria.\(^{20}\) Estimated frequency rates were termed either estimated incidence rates or estimated reporting rates, depending on the specific limitations of each data source used.\(^{20}\) Although the incidence of an adverse event is generally defined as its occurrence per 100 000 patients,\(^{20}\) given the relatively small numbers of patients from each data source used, estimated incidence was calculated as the ratio of the estimated frequency rate numerator and denominator.

Two sources of data were a literature report that summarized the results of ITP patients treated with anti-D IGIV in the clinical trial\(^6\) and a composite of clinical studies reported for ITP patients treated with anti-D IGIV.\(^{2,4,7,8,10,11,23}\) The raw data from each of these data sources were used as the respective numerators and denominators. FDA data were used as the numerator for the other frequency estimates, and drug utilization data obtained by the FDA\(^21,22\) were used for the denominator. Drug utilization data were from 2 IMS Health Incorporated databases: (1) Provider Perspective,\(^21\) 1995–1998, which provided prescription purchases by various US hospitals, health maintenance organizations, and other health care facilities\(^20\) and (2) National Disease and Therapeutic Index,\(^22\) 1995–1998, which provided prescription audits from US physician office-based practices.\(^{20}\) Conversion of the IMS data to the number of ITP patients treated with anti-D IGIV required certain broad assumptions that were referenced to anti-D IGIV literature to the extent possible.

**Results**

**Pretreatment profile of patients reported to the FDA**

The 15 cases of hemoglobinemia and/or hemoglobinuria that occurred following anti-D IGIV treatment were distributed across 13 states. None of the cases had attending physicians and health care facilities in common. The adverse events for these patients occurred between September 1995 and March 1999 and were reported to the FDA between May 1996 and April 1999.

The indication for treatment with anti-D IGIV was provided for all 15 patients. For 5 of the 7 pediatric patients, the indication was acute ITP following viral infection; for 1, the indication was not otherwise specified ITP; and for the other, the indication was not otherwise specified thrombocytopenia. For 4 of the 8 adult patients, the indication was chronic ITP; for 1, the indication was not otherwise specified ITP; for 2, the indication was not otherwise specified thrombocytopenia; and for the other, the indication was autoimmune hemolytic anemia.

One patient was diagnosed with autoimmune hemolytic anemia, and another patient had suspected autoimmune hemolytic anemia. Evan’s syndrome and autoimmune hemolytic anemia had been ruled out in 2 patients following a hematologic evaluation that was completed immediately prior to administration of anti-D IGIV. Two patients had preexisting renal insufficiency, and 1 patient had previously undergone a splenectomy.

The patients in the case study ranged in age from 3 to 86 years (Table 1). For pediatric patients, the mean age was 11 years (range: 3 to 17 years). The mean age of adult patients was 59 years (range: 32 to 86 years). Of the 7 pediatric patients, 4 were female. Of the 8 adult patients, 5 were female. Hemoglobins were available for all 15 patients, with a median of 117 g/L and a median of 119 g/L (range: 91 to 149 g/L).\(^{19}\)

The dose of anti-D IGIV administered was available for all 15 patients (Table 1). For the 12 patients whose hemoglobin level was greater than or equal to 100 g/L, the mean dose was 50 µg/kg, with a median dose of 50 µg/kg (range: 24 to 100 µg/kg). The 3 patients...
who had a hemoglobin of less than 100 g/L received a mean dose of 58 µg/kg, with a median dose of 52 µg/kg (range: 46 to 75 µg/kg). The anti-D IGIV infusion time was available for 5 patients; the mean infusion time was 15 minutes, with a median infusion time of 58 µg/kg, with a median dose of 52 µg/kg. The term PRBCs indicates units of PRBCs transfused. ΔHg indicates maximum difference between pretreatment and posttreatment serum creatinine levels in patients who experienced renal insufficiency. NA indicates not applicable.

*Preexisting renal insufficiency.
†Patient underwent renal dialysis.
‡Primary cause of death due to underlying disease.
§PRBCs ordered but patient refused transfusion.
‖Primary cause of death due to complications of posttreatment sequeleae.

Two patients who had a hemoglobin of less than 100 g/L received a mean dose of 58 µg/kg, with a median dose of 52 µg/kg (range: 46 to 75 µg/kg). The anti-D IGIV infusion time was available for 5 patients; the mean infusion time was 15 minutes, with a median infusion time of 24 minutes (range: 5 to 60 minutes).

ABO and D blood groups were available for 9 patients: 6 were group O, 3 were group A, and all were D-positive. Rh phenotyping was available for only 1 group O patient, who was DcDe. DATs were available for 7 patients, and 6 patients tested negative. The DAT of the patient with diagnosed autoimmune hemolytic anemia was positive for a cold-reacting antibody and complement. The DAT of the patient with suspected autoimmune hemolytic anemia was negative. No IATs were available.

Two patients who had previously received anti-D IGIV. One patient was treated approximately 6 months earlier without resulting hemoglobinemia and/or hemoglobinuria and with a plateau response; the other patient was treated 1 week earlier, without resulting hemoglobinemia and/or hemoglobinuria but without a plateau response. Of 12 patients for whom data were available, 4 had been previously treated with other blood products, which included PRBCs, platelets, and/or polyspecific IGIV, and none had experienced hemoglobinemia and/or hemoglobinuria following administration of those products. None of the patients received anti-D IGIV concomitantly with any blood products, and none of the patients subsequently rechallenged with anti-D IGIV.

Lot numbers were available for the anti-D IGIV administered to 9 patients. There were 10 different lots specified, and only 2 patients received anti-D IGIV from the same lot. For 4 lots reported, the FDA's database included 1 to 2 other adverse event reports that were unrelated to hemoglobinemia and/or hemoglobinuria.

### Posttreatment profile of patients reported to the FDA

The time of onset of signs and/or symptoms was available for 12 patients (range: 35 minutes to 4 hours). The most consistent sign available across all cases was hemoglobinuria, which was observed in 14 patients. When provided, the urine color ranged from pink to red to brown to black. The 1 patient who did not experience hemoglobinuria had an increased serum hemoglobin level and a serum haptoglobin at the lower limit of the normal range, although pretreatment results were not available for comparison. Seemingly, in this patient, whose hemoglobin level decreased 14 g/L, the degree of hemoglobinemia was not sufficient to deplete his serum haptoglobin and result in hemoglobinuria.

A continuum of symptoms was reported. Of the 12 patients for whom data were available, 2 patients did not experience any symptoms, while 10 patients exhibited classic symptoms associated with acute hemolytic transfusion reactions. At one end of the spectrum, 1 patient experienced shaking chills and low back pain but no sequelae. In contrast, another patient presented with no complaints other than “bloody urine,” which was later determined to be hemoglobinuria, but he experienced sequelae that included transfusion with PRBCs and the onset of renal insufficiency.

The mean decrease in hemoglobin was available for 14 patients (Table 1). The decrease in hemoglobin was not confounded by PRBC transfusion in only 8 of these patients; the maximum decrease in hemoglobin occurred in, at most, 1 week, with a mean decrease of 37 g/L and a median decrease of 34 g/L (range: 0 to 76 g/L).

Of note are the 2 patients who experienced the extremes of hemoglobin decreases. One patient developed black urine with 3+ blood and 0 RBCs/hpf within 3 hours following anti-D IGIV administration. Neither the degree nor the duration of hemoglobinuria was apparently sufficient to result in a hemoglobin decrease. In another patient, the maximum hemoglobin decrease occurred 8 days after treatment, but she experienced ongoing hemolysis for at least 20 days, as evidenced by persistent hemoglobinuria. Her hemoglobin decrease of 76 g/L may have been an underestimate of the degree of hemolysis. Hemolysis may have been moderated by an erythrokinetic response to anemia, which is suggested by a reticulocyte count of 21.4% 8 days after treatment.

The duration of hemoglobinuria or an approximation thereof was available for 8 patients (Table 1). Hemoglobinuria persisted 1 day or less in 2 patients, 2 days or more in 2 patients, 3 days or more in 1 patient, 7 days or more in 2 patients, and 20 days or more in 1 patient. Sequelae were not experienced in 3 of these patients, while each of the other 5 patients experienced 1 to 2 sequelae. The patient whose hemoglobinuria persisted 20 days or more experienced no sequelae.

Of the 8 patients whose decrease in hemoglobin was not confounded by PRBC transfusion, 2 patients experienced an estimated RBC loss less than or equal to that predicted by the dose of anti-D IGIV administered. The other 6 patients experienced a mean estimated RBC loss of 5.8 times that predicted by the dose of anti-D IGIV administered, with a median loss of 5.7 times that predicted (range: 3.0 to 8.5 times that predicted). At one extreme, the patient whose hemoglobin decreased 76 g/L and whose hemoglobinuria persisted 20 days or more experienced an estimated RBC loss 3.0 times that predicted by the 100 µg/kg dose of anti-D IGIV she was given. At the other extreme, another patient experienced a 27-g/L hemoglobin decrease and hemoglobinuria that cleared within 7 hours, but his estimated blood loss was 8.5
times in excess of that predicted by the 53 µg/kg dose of anti-D IGIV he received.

Of the 15 total patients, 4 experienced no sequelae. The remaining 11 patients experienced at least 1 sequela that was attributed to anti-D IGIV administration, and 6 patients experienced various combinations of 2 to 3 concurrent sequelae.

PRBCs were ordered for 7 patients; 1 patient refused transfusion, and thus only 6 patients were transfused (Table 1). The mean number of units of PRBCs transfused within hours to days of anti-D IGIV administration was 3 (range: 1 to 6 units). When specified, patients were transfused with D-negative PRBCs.

Onset or exacerbation of renal insufficiency was noted in 8 patients: 6 patients had pretreatment renal function within normal limits, and 2 patients had preexisting renal insufficiency. Paired pretreatment and posttreatment serum creatinine levels were available for 7 of these patients. The mean increase in the serum creatinine level was 35 mg/L, with a median increase of 25 mg/L (range: 8.0 to 103 mg/L) (Table 1). The mean time of onset of the renal insufficiency was approximately 22 hours (range: approximately 2 to 48 hours) following anti-D IGIV administration. In surviving patients who did not undergo dialysis, the serum creatinine level peaked within a mean of 5 days (range: 2 to 9 days) and resolved, as evidenced by the return of the serum creatinine level to baseline, within a mean of 12 days (range: 4 to 23 days). Two patients died with unresolved renal insufficiency. No renal histology was available since neither renal biopsies nor autopsies were performed on any of these patients.

The 17 mg/L peak serum creatinine level for 1 patient belied the fact that he presented with oliguria; this suggests that he responded to promptly administered medical intervention. The patient whose peak serum creatinine level was 110 mg/L and who underwent dialysis 3 times had pretreatment renal function that was within normal limits.

DATs were available for 7 patients and were obtained 24 to 72 hours after treatment. Results of 3 DATs were reported only as positive, and 4 were reported as positive for IgG and negative for complement. Elutions, available for 3 of the latter 4 DATs, revealed only anti-D. Of possible note is that hemoglobinuria was ongoing for these 3 patients at the time the DATs were obtained. IATs, available for 3 patients, were negative for 2 patients and positive for anti-C in the known C-negative patient. The results of the latter 3 DATs and the 1 IAT appear to reflect passively acquired anti-D and anti-C, respectively. But these results do not exclude the possibility that other IgM-, IgG-, and/or complement-sensitized RBCs may have been present at the onset of hemoglobinemia and/or hemoglobinuria but were not detectable 24 to 72 hours posttreatment.

Platelet response following anti-D IGIV treatment was available for 9 patients; 5 patients exhibited an increase in platelet count that ranged from 75 000-341 000 × 10⁹/L, which was observed 3 to 7 days after treatment. Of the 4 patients who did not exhibit a platelet response, 2 had not experienced an increase in platelet count by 1 week posttreatment, after which no further platelet counts were available, and 2 had not experienced an increase in platelet count at 6 weeks posttreatment. However, the hemoglobinemia and/or hemoglobinuria did not preclude a platelet response in the 5 patients.

Four patients died following anti-D IGIV administration (Table 1). One patient died 3 days following treatment with anti-D IGIV due to pulmonary edema and respiratory distress that resulted from exacerbation of anemia; her physician believed that she would probably have survived had she not refused transfusion. Three patients died from other primary causes 2 to 22 days posttreatment. Although not directly related to the primary cause of death in these 3 patients, the extent to which the 1 to 2 sequelae experienced by each may have exacerbated their conditions and contributed to their deaths is unknown.

**Frequency estimates of hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration for the ITP indication**

Three sets of frequency estimates (Table 2) were calculated. In the literature report based on the clinical trial, 2 of 137 ITP patients experienced hemoglobinemia and/or hemoglobinuria following administration of anti-D IGIV. The incidence rate of hemoglobinemia and/or hemoglobinuria associated with anti-D IGIV administration was estimated at 1.5%, with an estimated incidence of 1 case of hemoglobinemia and/or hemoglobinuria per 69 ITP patients treated with anti-D IGIV. From the composite of clinical studies in the literature involving 528 ITP patients, there were no patients reported to have experienced hemoglobinemia and/or hemoglobinuria in association with anti-D IGIV administration, thereby yielding 0 as the estimated incidence rate and the estimated incidence. Based on FDA and IMS data for the time period of March 1995 to December 1998, 13 cases of hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration for the ITP indication were reported. During that period, an estimated 14 500 patients were treated with anti-D IGIV indication, corresponding to a 0.1% estimated reporting rate and an estimated incidence of 1 in 1115.

**Discussion**

**Case series patients reported to FDA**

The extent to which the 15 case series patients were representative of the population of ITP patients is indeterminate. For the 11 patients whose presenting diagnosis was ITP, information was generally unavailable concerning the criteria employed to diagnose ITP and whether or how differential diagnoses had excluded other hematologic or medical causes of thrombocytopenia. For the patients whose indication for treatment with anti-D IGIV was not otherwise specified thrombocytopenia, the presenting diagnosis was unavailable and may or may not have been ITP. For patients whose presenting diagnosis may not have been ITP, for the patient

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Reported patients experienced hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration during a specified time period. Total patients were treated or estimated to have been treated with anti-D IGIV during a specified time period. NA indicates not applicable. Data for the clinical studies are cited in references 2, 4, 6-8, 10, 11, and 23.

*Data on file, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA, Rockville, MD; March 1995-Decem-ber 1998.
whose indication for use was autoimmune hemolytic anemia, and for the patient who had previously undergone splenectomy, the basis on which physicians decided to treat them off-label with anti-D IGIV was unknown.

Limitations of the above data notwithstanding, the merit of this case series is that it describes clinical and laboratory findings associated with acute onset hemoglobinemia and/or hemoglobinuria following treatment of patients with anti-D IGIV for the ITP indication. Furthermore, the case series notes the occurrence of treatment-associated sequelae that are not explicitly specified in the package insert that was current at the time of this review and that have not been previously reported in the literature (Dr M. Tarantino, personal communication, June 1999).2,4-8,10,11,13,14,23

Had this case series review been a prospective instead of a retrospective analysis, the case definition would have specified diagnostic criteria for inclusion or exclusion of patients. Supplemental laboratory data would have been obtained including, among others, Rh phenotypes, appropriately timed pretreatment and posttreatment serum hemoglobins, haptoglobins, and complements as well as DATs, elutions, and IATs. Additionally, ITP patients who did not experience hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration would have been included as a control group. Had all such data been available, multivariate statistical analysis could have been used to examine for possible relationships between and among variables for inferences about patients at risk for hemoglobinemia and/or hemoglobinuria as well as patients at risk for treatment-associated sequelae.

Frequency of hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration for the ITP indication

Given the proprietary nature of clinical trial data, the only such data available for this review were for the subset of 137 patients published in the literature.6 Whether all patients were monitored for hemoglobinuria and/or hemoglobinemia or whether it was only coincidentally observed was not reported. The extent to which the clinical trial patients were representative of the population of ITP patients is unknown, given the potential bias that may exist in clinical trials.20,24 The frequency estimates from the clinical trial might have differed if calculated from data for the total sample of 257 clinical trial patients referenced in the package insert.1

None of the 528 ITP patients in the clinical studies2,4,7,8,10,11,23 were reported to have experienced hemoglobinemia and/or hemoglobinuria after treatment. However, from the information provided, the possibility cannot be excluded that hemoglobinemia and/or hemoglobinuria occurred but was unrecognized, not perceived as an adverse event, or did not exceed the threshold for reporting as an adverse event. Furthermore, the extent to which the patients were representative of the population of ITP patients is unknown, as diagnostic criteria for patients were not generally reported.

There is acknowledged underreporting in passive surveillance adverse event reporting systems such as the FDA system.20,22 Aside from this, it is likely that FDA data further underestimated the number of cases due to the lack of recognition of hemoglobinemia and/or hemoglobinuria by attending or consulting physicians. This problem occurred in 5 of the 15 case series patients. In addition, insufficient data were available to evaluate 6 other possible cases of hemoglobinemia and/or hemoglobinuria against the case definition. Although the assumptions used to translate the IMS data into an estimated number of ITP patients treated with anti-D IGIV were referenced in the literature to the extent possible,2,4,7,20,25-27 these assumptions may nonetheless have been invalid.

Studies or reports involving between 5 and 1842 infusions of anti-D IGIV and between 20 and 261 ITP patients provided one frame of reference for evaluating the frequency estimates calculated. In those studies and reports, the estimated incidence rates for all adverse events attributed to anti-D IGIV treatment ranged from 1% to 16%.1,2,4,6,8,27 When compared with the magnitude and marked variability of these estimated incidence rates, the frequency estimates of 1.5% from the clinical trial and 0.1% from the FDA and IMS data seem plausible. Although the estimated frequency rates of the clinical trial and the FDA and IMS data cannot be construed as actual incidence rates, they provide first approximations against which physicians may be able to preliminarily assess the risk–benefit ratio of treating ITP patients with anti-D IGIV.

Between May 1999 and October 1999, subsequent to the time period of this review, the FDA received an additional 26 anti-D IGIV adverse event reports of possible or probable hemoglobinemia and/or hemoglobinuria in ITP patients. Follow-up is in progress to obtain supplemental data to further evaluate these cases against the case definition. These additional cases appear to affirm that hemoglobinemia and/or hemoglobinuria in the case series patients was not a spurious occurrence. Use of anti-D IGIV for the treatment of ITP has continued to increase in the United States since licensure,21,22 which may be attributed to factors such as efficacy, safety, cost, and availability.2,4,5,7,9,11,13,14,26-28 Thus, the potential exists for continued occurrence of anti-D IGIV-associated hemoglobinemia and/or hemoglobinuria and sequelae.

Mechanism(s) of hemoglobinemia and/or hemoglobinuria following anti-D IGIV administration for the ITP indication

The primary mechanism of action of anti-D IGIV and the temporal association between anti-D IGIV administration and the onset of hemoglobinemia and/or hemoglobinuria suggest a causal relationship in the clinical trial and in the case series patients. However, neither the literature nor the case series data confirm or rule out this presumed causality on the basis of established mechanisms of immune-mediated hemolysis. If attributable to anti-D, the mechanism by which hemoglobinemia and/or hemoglobinuria occurs is unexplained given the relatively limited number of D antigens per RBC27,29-31 and the distance between these antigens, which exceeds the span of IgG anti-D7,30-32; the generally noncomplement-fixing behavior of anti-D2,7,30-33; and the relative lack of complement activators in anti-D IGIV5,6,17,18. The literature and case series data do not definitively indicate whether hemoglobinemia and/or hemoglobinuria is attributable to intravascular hemolysis, extravascular hemolysis, or both.5,12,23,29-31,33

Other mechanisms or explanations could be responsible for precipitating, accompanying, or potentiating hemoglobinemia and/or hemoglobinuria, although they were not evaluated. Possible mechanisms or explanations include concomitant diagnoses associated with immune-mediated hemolysis, either not reported or not yet diagnosed, such as autoimmune hemolytic anemia and Evan’s syndrome12,29,30; Rh phenotype, which determines the number of D antigens/RBC29,32 and may influence the degree of anti-D–mediated hemolysis23,34; splenic saturation and correspondingly diminished capacity for clearance of anti-D-sensitized RBCs29,30; concentrations of IgG1, IgG3, protein aggregates, and/or anti-
idiotype antibodies in anti-D IGIV, which may form complement-fixing immune complexes in vivo (Dr R. Grimes, personal communication, May 1999)14,16,18,27,29,30, and conditions of storage and reconstitution of anti-D IGIV, among others.27

It has been suggested that more than one mechanism may be responsible for the platelet response of ITP patients treated with anti-D IGIV.5,8,10,12,16 Similarly, multiple mechanisms and explanations may occur or interact to result in hemoglobinemia and/or hemoglobinuria. Furthermore, different mechanisms or explanations may account for this occurrence in different patients. Unquestionably, further research and more data are needed to clarify the mechanism(s) or explanation(s) involved.

Implications for treatment of ITP patients with anti-D IGIV for the ITP indication

The results of this case series suggest that patients treated with anti-D IGIV for the ITP indication should be closely monitored for signs and symptoms of hemoglobinemia and/or hemoglobinuria, clinically compromising anemia, and renal insufficiency. Although no other sequelae were noted in the clinical trial literature report or in the patients reported to the FDA, hemoglobinemia and/or hemoglobinuria has been associated with other clinical complications, notably disseminated intravascular coagulation,30,32,35 and patients should be monitored for signs of this and other possible sequelae.

When transfusion with PRBCs is indicated in the presence of ongoing hemoglobinemia and/or hemoglobinuria, physicians may wish to consider transfusion with D-negative PRBCs.30,32,35 Platelet concentrates as well as apheresis platelets may contain 0.5 to 5.0 mL of RBCs26,32,35; hence, caution may be appropriate if platelets from D-positive donors are transfused during episodes of hemoglobinemia and/or hemoglobinuria.

The FDA encourages physicians and other health care professionals to report cases of hemoglobinemia and/or hemoglobinuria following administration of anti-D IGIV for the ITP indication either to the manufacturer or directly to the FDA. Adverse events related to anti-D IGIV or any other FDA-licensed or FDA-approved product may be reported to the FDA's adverse event reporting system, MEDWATCH, by any of the following methods: telephone (1-800-FDA-1088); fax (1-800-FDA-0178); mail (MEDWATCH, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787); or the Internet (http://www.fda.gov/medwatch).

Acknowledgments

The author wishes to thank the physicians and other health care professionals who reported these adverse events to the FDA and/or to the manufacturer and whose tireless and repeated reviews of patients’ charts provided the data for this case series. Unfortunately, due to the many individuals involved, they cannot be acknowledged individually. The author would also like to express appreciation to Drs Susan Ellenberg, Marcel Salive, Richard Kapit, Jerome Donlon, Dorothy Scott, Basil Golding, and Ellen Lazarus from the Center for Biologics Evaluation and Review, FDA, Rockville, MD, for their review of this manuscript; to Joslyn Swann and Katrina Garry from the Center for Drug Evaluation and Research, FDA, Rockville, MD, for providing the raw IMS data and obtaining its clearance, respectively; and to Karen Cipolone, Karen Kiekhaefer, and Sharon Moore from the Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD, for their input.

References


34. Zimmerman SA, Combs MR, Issitt PD, Ware RE. The number of erythrocyte D antigen sites is a predictor of clinical response to anti-D in children with immune thrombocytopenic purpura [abstract]. Blood. 1997;90(suppl 1, part 2):458a.

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