RhIG for the treatment of immune thrombocytopenia: consensus and controversy

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Anti-D immune globulin (RhIG) is a front-line option in North America for the treatment of immune thrombocytopenia (ITP) in children and adults. Recently, addition of a Food and Drug Administration-mandated black box warning highlighted the risks of intravascular hemolysis, renal failure, and disseminated intravascular coagulation after anti-D infusion, prompting concern within the medical community regarding its use. A working group convened in response to this warning to prepare a consensus document regarding the safety of RhIG because there has been no increased incidence of adverse events since the initial discovery of these reactions many years ago. The efficacy of anti-D is well documented and only briefly reviewed. The estimated incidence and proposed mechanisms for the rare, major treatment-related complications are discussed, and signal detection data associated with heightened risk of acute hemolytic reactions are presented. The importance of considering host factors, given the rarity of severe reactions, is emphasized. Safety profiles of parallel treatment options are reviewed. The working group consensus is that RhIG has comparable safety and efficacy to other front-line agents for the treatment of children and adults with ITP. Safety may be further improved by careful patient selection.

Immune thrombocytopenia (ITP) results when an unknown trigger causes development of an autoantibody (predominantly immunoglobulin [Ig]G) recognizing one or more platelet (PLT) glycoproteins, with subsequent generation of polyclonal autoantibodies against multiple PLT glycoproteins through the process of epitope spreading.[1] These antibody-coated PLTs are efficiently cleared by the reticuloendothelial system (RES), resulting in varying degrees of thrombocytopenia. Recent studies have suggested additional, more complex mechanisms causing or contributing to thrombocytopenia including antibody-mediated inhibition of thrombopoiesis,[2-4] T-cell dysregulation contributing to persistence of the autoimmune response,[4,5] cytotoxic T-cell

ABBREVIATIONS: AHR = acute hemolytic reaction; ARF = acute renal failure; DIC = disseminated intravascular coagulation; EBV = Epstein-Barr virus; ITP = immune thrombocytopenia; IVH = intravascular hemolysis; RES = reticuloendothelial system; RhIG = anti-D immune globulin.

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responses,[6,7] and inadequate thrombopoietin levels for the degree of thrombocytopenia.[8-10] In some patients, hemorrhage may result in substantial morbidity and rarely life-threatening bleeding. Profoundly thrombocytopenic patients may have a significant decrease in their energy levels and activity restrictions due to bleeding risk and other ill-defined factors, which adversely affect their health-related quality of life.[11]

Anti-D immune globulin (RhIG) is a front-line agent for the treatment of ITP, with demonstrated efficacy. A response rate of approximately 60% to 72% has been reported,[12-15] as measured by significant improvement in circulating PLT count. At a dose of 50 to 75 μg/kg, RhIG has been shown to be as efficacious as intravenous immune globulin (IVIG) for children with ITP.[15,16] Based on the mechanism of action, a small amount of extravascular hemolysis is known to be an expected consequence of treatment, which has been well tolerated in the majority of otherwise healthy and nonanemic recipients.[12,16-18] Other infusion-related side effects such as headache, fever, chills, and vomiting are generally mild and transient and are lessened or alleviated with the routine use of premedications such as acetaminophen, diphenhydramine, corticosteroids,[19] and if necessary, ondansetron.

Rare cases of exaggerated hemolysis were reported to the Food and Drug Administration (FDA) soon after RhIG was licensed in the United States.[20] With increased use of the agent, additional cases of severe hemolysis, as well as disseminated intravascular coagulation (DIC) and renal failure have been seen.[21] Recently, an FDA-mandated black box warning was issued for all IV RhIG products, highlighting the risk of these events after treatment with anti-D preparations.[22] At the instigation of Cangene BioPharma, an expert panel was convened to evaluate the role for RhIG for the treatment of ITP in face of the increased concern among medical providers with use of this agent.

METHODS

The panel consisted of seven experts with extensive cumulative experience with RhIG therapy for the treatment of pediatric and adult ITP. The members convened to discuss aspects of ITP pathophysiology and treatment and where RhIG fits into the available treatment options for patients with ITP, considering the heightened safety concerns. A disproportionality analysis was conducted by classifying all adverse events reported to Cangene BioPharma for the indication of ITP as either "hemolytic" or "without evidence supporting hemolysis." This statistical approach is useful in adverse event surveillance, as it allows for calculation of the observed and expected incidence of a specific drug-event combination.[23] A literature search for published data on adverse events after RhIG administration was performed. Reports describing safety profiles of other front-line treatment options for ITP were also reviewed.

HISTORY OF RHIG USE IN ITP

The benefits of intravenous infusions of gammaglobulin (IVIG) on thrombocytopenia were first observed in children with primary immunodeficiency and have been attributed to inhibition of RES-mediated destruction of antibody-coated PLTs. Efforts to block immune-mediated PLT destruction in patients with primary ITP by infusing gammaglobulin led to the use of IVIG in the treatment of children at all stages of primary ITP as initially reported in 1981.[24] In the following years, the use of IVIG expanded to adults and children with acute and chronic ITP.[25-27] Despite uncertainty regarding the mechanisms of action of IVIG for the treatment of ITP, RES blockade, at least in part by up regulation of FcγRIIB likely occurs,[28] and IVIG effectively increases the circulating PLT count in at least 70% to 80% of patients. The observation that treatment with IVIG was often associated with mild hemolysis[29] led to the first efforts to target the red blood cell (RBC) D antigen directly using RhIG in patients with ITP.[30]

WinRho was developed in 1972 at the Winnipeg Rh Institute using the Hoppe and colleagues[31] method of preparing anti-D IgG for IV use through ion-exchange chromatography, as an alternative to intramuscular injection of anti-D for the prophylaxis of Rh disease.[32] The benefits of this approach, used since the 1960s outside the United States, included improved efficacy due to IV administration, greater product yield, and a better safety profile due to markedly decreased amounts of other plasma proteins (non-IgG) that had been shown to aggregate and fix complement in other preparations.[32] Several highly sensitized women who had previously had infants die of Rh disease were the initial plasma donors. As currently produced, RhIG is a pooled plasma product composed of human anti-Rh_oD IgG purified from plasma obtained from hyperimmunized Rh_oD– male donors.[32]

Although initially developed for prophylaxis of Rh disease, the seminal work of Salama and Mueller-Eckhardt inspired the use of RhIG for the treatment of ITP in the United States and Canada in 1986, with active trials beginning in 1987.[33] Rh_oD immune globulin (Cangene BioPharma) received FDA approval for the treatment of ITP for nonsplenectomized, D+ patients in 1995. The likely mechanism of action of RhIG involves the opsonization of endogenous Rh_oD+ RBCs with anti-D, resulting in preferential RES clearance of coated RBCs, thereby allowing antibody-coated PLTs to remain in circulation.[18] In addition to RES blockade by competitive inhibition of F_c receptors, additional mechanisms of action have been proposed, including cytokine stimulation[34] resulting

TABLE 1. Reported AHRs and total infusions per year since licensure

Year	Number of cases reported to the FDA	Estimated total number of infusions	Estimated incidence (%)
1995-1997	5	23,775	0.02
1998-2000	15	50,109	0.03
2001-2003	17	58,976	0.03
2004-2006	17	57,379	0.03
2007-2009	16	38,761	0.04

in paralysis of phagocytosis, anti-idiotype antibodies, and F_c receptor modulation.[35]

RhIG USE IN THE CURRENT ERA

RhIG has been widely used since 1995, with more than 225,000 infusions estimated to have been administered since FDA approval. Overall, there have been relatively few serious adverse events (Table 1) and comparable efficacy to IVIG.[15,36] The advantages of RhIG therapy compared to IVIG include substantially shorter infusion time, markedly smaller infusion volume, longer duration of response demonstrated in HIV-infected patients with ITP, variably lower cost, and exposure to 1/100th as many donors per dose.[14,32] As a result of the extravascular hemolysis that occurs in the several days after administration, an approximately 1 to 2 g/dL decrease in hemoglobin (Hb) concentration is expected and is usually well tolerated in patients who are not acutely ill and have no baseline anemia or predisposition toward hemolysis. The serious side effects discussed above such as exaggerated hemolysis, DIC, and acute renal failure (ARF) have been infrequently reported, and the mortality rate is very low (Fig. 1). A US FDA-mandated black box warning has been issued for all RhIG preparations related to these events.[22]

When rare but serious adverse events occur with a treatment, they must be carefully considered when contemplating management options for an individual patient. It is important to note that no treatment option for ITP is without risk of serious side effects and the comparative frequency of "rare" events may be difficult to evaluate. The nonbleeding patient at low risk of hemorrhage might be best managed by close observation alone.[37] For the bleeding or high-risk patient, there is little debate that therapy to increase the circulating PLT count is justified.[38] The task for the practitioner is to identify the treatment option best suited for a particular patient, keeping in mind the safety profile of each available agent in addition to the response profile.[17,19,39]

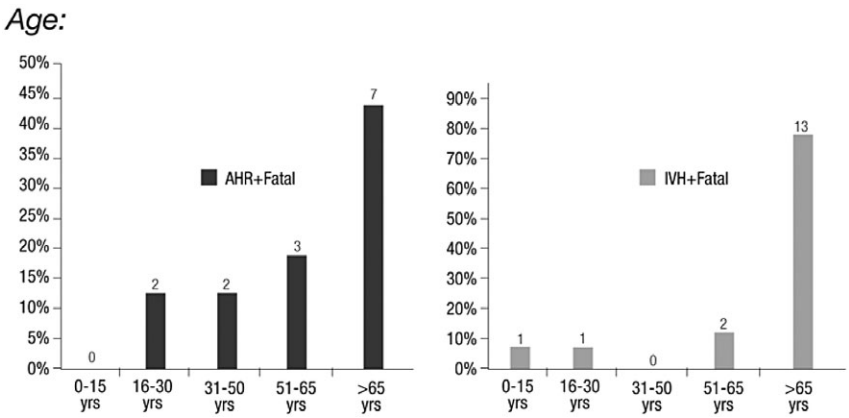

Fig. 1. Rate of mortality by age after event classified as (A) AHR and (B) IVH.

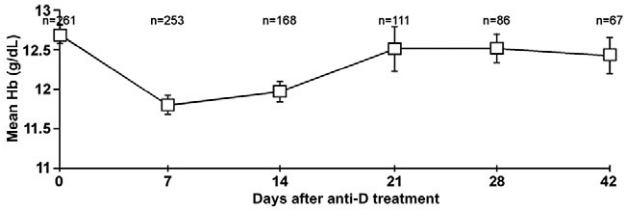

Fig. 2. Hemolysis with anti-D: (A) Mean Hb concentrations with time after infusion of anti-D. Shown is mean ± SD. n = number of subjects. Reproduced from Scaradavou et al. (1997), with permission from the American Society of Hematology.[14]

SERIOUS ADVERSE EVENTS

Hemolysis

A decrease in Hb concentration of 0.5 to 2 g/dL over the 3 to 7 days after RhIG infusion occurs in the majority of treated patients. This amount of hemolysis is typically well tolerated, with recovery to baseline counts usually within 3 weeks after administration (Fig. 2).[14] As the frequency of use of RhIG therapy increased in the decade after licensure, reports of exaggerated hemolysis emerged. In 1998, a report of seven cases of hemolysis was published,[40] followed in 2000 by an FDA report of 15 cases.[20] These 15 cases were classified as intravascular hemolysis (IVH), due to the presence of hemoglobinemia and/or hemoglobinuria. If clinically significant hemolysis occurred in the absence of hemoglobinemia or hemoglobinuria, or these tests were not performed, the case was categorized as an

acute hemolytic reaction (AHR). Although these events are very infrequent compared to the total number of patients who have received the drug, the reports have heightened awareness about excessive hemolysis since they have been associated with a risk of mortality (Fig. 1).

The actual incidence of serious complications associated with RhIG infusion has not changed significantly since FDA approval (Table 1), but with increased use, additional cases have been reported. The currently accepted estimate for the incidence of severe hemolytic reactions (defined as a relatively rapid Hb decrease along with at a minimum hemoglobinemia or hemoglobinuria) is 1:1115 patients.[20]

The mechanism underlying the development of severe hemolysis with hemoglobinemia or hemoglobinuria remains elusive. In principle, D antigen sites on the RBC are relatively sparse (5-30,000/cell compared to up to 1.8 million for A or B sites) and do not cap (move together) in the membrane as a result of the multiple transmembrane domains that compose their structure. Two molecules of anti-D IgG cannot bind closely enough together (300 Å) to fix and activate C1q to initiate the classical pathway of complement.[41-43]

To investigate whether this process could be specifically attributed to production lot differences in amounts of other alloantibodies, Gaines and colleagues[44] evaluated several different lots of RhIG and blood samples from patients who had experienced an episode of severe hemolysis and performed an in vitro hemolysin assay. These results could not substantiate that IVH had taken place or that the process could be attributed to identifiable differences in the product lots. Furthermore, no specific lots were implicated in these cases as no clusters of reactions were reported with any particular lot, suggesting that the severe reaction is more dependent on recipient rather than donor factors. It is possible, however, that other alloantibodies in the product that are not detectable by routine methods could be present and could cause rare patients to exhibit such severe manifestations, such as the presence of trace amounts of anti-D IgM.

Multiple investigations of these cases have been performed, in an effort to understand the pathophysiology of the brisk hemolytic process. Complement-mediated IVH had been considered the likely pathophysiology, but available evidence supports the hypothesis that RhIG does not appreciably fix complement.[45] Another possibility is that certain patients are "overexpressors" of certain antigens. This has been well described for blood group B antigens, and D antigen expression varies according to the Rh haplotype.[35] If rare patients have a phenotype of dense or proximal D antigens, then otherwise pharmacologically effective levels of RBC antibodies in RhIG could contribute to severe hemolysis in a lot-independent fashion.

Finally, it is possible that genetic differences in proteins involved in RES-mediated clearance contribute to excessive hemolysis. Other hypotheses such as oxidative stress, mutations in regulatory proteins such as CD55 and CD59, transfer of D antigen to bystander RBCs by microparticles resulting in increased D antigen density, and development of HLA antibodies have been proposed but seem less likely.

Perhaps the most plausible explanation is that in the setting of brisk hemolysis, the RES is "overwhelmed" and thus the extravascular hemolysis exceeds the capability of the RES to clear the RBCs and their contents, thereby allowing free Hb to spill into the plasma and urine. In this scenario, true IVH does not actually occur.[45] Haptoglobin and hemopexin would be readily depleted by intravascular Hb and heme, respectively. It is clear that more research is needed to better understand the rare occurrence of exaggerated hemolysis after RhIG administration. A complicating factor is that the intensity of these severe reactions may affect the relationship between the patient and the treating hematologist, making the obtaining of subsequent samples very difficult.

DIC

The risk of DIC after the administration of RhIG was highlighted in a 2005 publication of six cases reported to the FDA.[21] Gaines detailed the findings of acute hemolysis and DIC in five adults and one child. Although the child recovered without long-term sequelae, all five adults died. One of the five patients had previously received RhIG without complications. The actual incidence of these events is unknown, but estimated by Gaines to be less than 1 event per 20,000 doses.[21] The mechanism by which DIC occurs is unknown, but one postulate is that it may be due to acquired antibodies to blood group antigens, although more than 90% of the RhIG product has been shown to be anti-D IgG.[32] RBC stroma may activate the coagulation system, a probable mechanism for the increased thrombosis seen in patients with thalassemias.[46]

ARF

ARF has also been described after RhIG infusion.[20,40,47-49] In these isolated cases, acute hemolysis is thought to lead directly to ARF, and most patients have had complicating factors predisposing to renal failure. Risk factors for ARF after RhIG include baseline elevated serum creatinine and acute Epstein-Barr virus (EBV) infection.[50,51] Both younger patients and adults with this complication have required dialysis.[47,49] Renal function has typically returned to baseline after appropriate management. The presumed mechanism of ARF after RhIG is immune hemolysis with subsequent renal tubular toxicity from free Hb in predisposed hosts. The precise mechanism of exaggerated hemolysis and ARF after anti-D administration in the setting of EBV infection is not known, but may be related to broad activation of the immune system and polyclonal B-lymphocyte expansion.

Acute respiratory failure

The frequency of transfusion-related acute lung injury (TRALI) after RhIG administration is not known, but appears to be even lower than severe hemolysis and ARF. There has been at least one case reported.[52] Acute respiratory failure in the context of acute hemolysis has been reported infrequently in the elderly population and is most commonly attributed to worsening of congestive heart failure with pulmonary edema and subsequent cardiorespiratory decompensation.

SIGNAL DETECTION: RISK FACTORS FOR SEVERE REACTIONS

A closer look at the patients reported to have had severe hemolysis, renal failure, and/or DIC after receiving RhIG reveals that the majority of patients experiencing severe complications had important comorbid conditions at the time of treatment (Fig. 3).[20,21,53] Comorbid conditions that occurred frequently included existing autoimmune hemolytic anemia, underlying renal insufficiency, underlying malignancy, and acute or recent EBV infection (Table 2). The risk of administering RhIG in the setting of active or recent EBV infection has been highlighted.[50] Another potential contributing factor is cirrhosis.

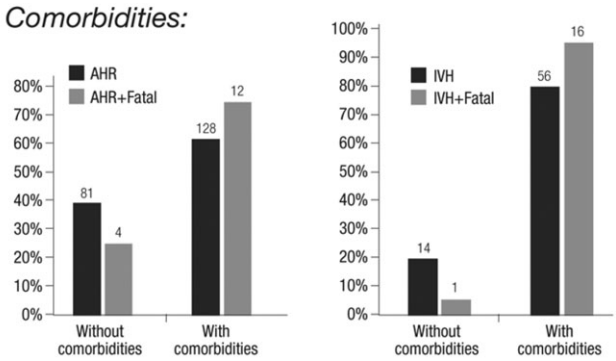

Fig. 3. Rate of AHR after RhIG administration and associated mortality by comorbidities.

To date, 14 years (1995-2009) of adverse events reported to the manufacturer have been analyzed by Cangene BioPharma, in an effort to determine if certain risk factors might predispose specific patient populations to AHRs after administration of RhIG. The results of the analysis (Table 2) offer insight into comorbid conditions that may predispose some populations to an AHR. This disproportionality analysis was conducted by classifying all adverse events reported to Cangene BioPharma for the ITP indication (n = 683) into two categories: 312 that were hemolytic and 371 without evidence supporting hemolysis. Conditions reported to be associated with acute hemolysis, summarized in Table 2, consist of active viral infections (EBV, hepatitis C virus [HCV]), hematologic malignancies (non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukemia), and autoimmune disorders (autoimmune hemolytic anemia, systemic lupus erythematosus, antiphospholipid syndrome).

Although AHRs have been reported in all age groups, there is a general increase in frequency of fatal reactions with advancing age (Fig. 1) with approximately 45% of fatalities having occurred in adults above the age of 65 years. This increased mortality is most likely due to the presence of underlying conditions in older adults, which may be aggravated by brisk hemolysis (Fig. 3).

RHIG AND IVIG

Because IVIG and RhIG are frequently considered front-line treatment options and are both pooled plasma immunoglobulins, the adverse event profile of IVIG is reviewed here. IVIG is a pooled human plasma product that contains predominantly IgG, similar to IV anti-D, which is a hyperimmune IVIG preparation. IVIG use is associated with infusion-related side effects including hemolysis. As mentioned previously, at least a minor degree of hemolysis commonly occurs after IVIG treatment.[29] However, there are rare reports of significant decreases in Hb concentration (between 3 and 5 g/dL) after the administration of IVIG.[54-56] There are occasional "epidemics" reported related to specific products as happened recently in Canada.[57] The mechanism of hemolysis is unclear, but may be related to the passive transfer of blood group or minor antibodies, a hypothesis supported by the increased risk in non-O blood group individuals. IVIG is known to contain a range of titers of anti-A (up to 1:64) and anti-B (up to 1:8) and also contains anti-D, and the amount of antibody transfused by a given lot is dose related.[57-60] Hemolysis after RhIG infusion has not been linked to ABO blood group, likely

TABLE 2. Disproportionality analysis of risk factors for AHRs versus nonhemolytic adverse events

Risk factors	AHR, % (n = 312)	NHR, % (n = 371)	p value
Infections	24	7	<0.0001
Viral infections	20	5	<0.0001
EBV	6	1	<0.0001
HCV	4	1	0.076
Other viral infections	10	2	<0.0001
Nonviral infections	8	4	0.0078
Neoplasms	17	8	<0.0001
Leukemia and lymphoma	9	3	<0.0001
Nonhematologic	7	4	0.0539
Autoimmune disorders	6	2	0.0195

due to the small amount of antibody infused. Severe hemolysis leading to systemic complications, including ARF requiring hemodialysis[56] and DIC,[59] have been reported after IVIG administration.

Renal failure after IVIG administration has been reported to the FDA in more than 120 patients. The development of renal failure appears to be largely related to the osmotic load associated with IVIG infusion because approximately 60% of the cases of ARF were associated with a single preparation of IVIG that is no longer used. In this recently retired preparation, sucrose was used to stabilize it to prevent aggregate formation; the osmolar load resulted in an osmotic nephrosis causing tubular vacuolization, swelling, and necrosis.[61] However, not all patients with renal failure after IVIG infusion have similar pathologic findings on biopsy and the mechanism of renal failure in these patients is less clear.[62] At least one patient had hemolysis with hemoglobinemia and hemoglobinuria contributing to renal failure.[56] Most cases of ARF after IVIG resolved, although 36% of patients required dialysis for some period of time.[63] Moreover, the renal adverse events may have contributed to the death of 15% of patients who died.[63]

Additionally, due to the large numbers of donors pooled to form the product, IgG dimers are known to form and are thought to be a result of idiotype–anti-idiotype complexes.[64] Formation of aggregates occurs, although less frequently and at a much lower level. The IgG aggregates and possibly the IgG dimers can fix complement. Although extensive effort is made to remove the aggregates during processing, they have not been completely eliminated and may still contribute to infusion-related toxicity, although probably not hemolysis.[65] The dimers (apparently idiotype–anti-idiotype in composition) cannot be removed.

Other significant concerns include the potential for fluid overload due to the infusion of large volumes, although the oncotic load of IgG per molecule is only one-sixth that of albumin. In addition, there are rare but potentially life-threatening complications including TRALI,[66] aseptic meningitis, anaphylaxis in the setting of IgA deficiency, thromboembolism including hepatic venoocclusive disease or myocardial infarction and stroke, and infectious disease transmission.[61]

The similarity of the reports of hemolysis and other adverse events such as thromboembolism after IVIG administration provide a historical context for the recent focus on these reactions associated with IV anti-D used to treat ITP. It is unclear if the reactions from IVIG are due to the same mechanisms as those associated with RhIG. Given the lack of a similar focus on tracking these events associated with IVIG, the incidence and severity appear not inconsistent with that seen with IV RhIG, but remain anecdotal as a result of the lack of systematic tracking of these events. The comparative frequency of adverse events of a number of other treatments are illustrated in Fig. 4.

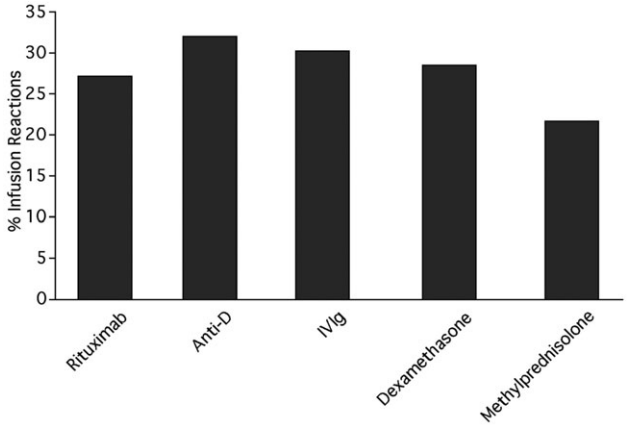

Fig. 4. Rate of infusion reaction with various therapies to treat ITP. Reproduced from Cooper and Tarantino (2009), with permission from the International Society of Thrombosis and Haemostasis.[39]

PANEL RECOMMENDATIONS

Definitions

Several publications, as well as the black box warning on RhIG product inserts,[22] define the episodes of severe hemolysis as "intravascular hemolysis." To date, no evidence has been produced that substantiates the presence of RBC destruction within the vasculature. The process of IVH is typically considered to be present when hemoglobinemia and/or hemoglobinuria are found, but findings of free Hb in the plasma or urine are not limited to IVH. When IVH is caused by an antibody-mediated process, it typically involves complement fixation. Antibodies against the A and B blood groups are the most likely antibodies to fix complement, and antibodies against certain other RBC antigens have not been shown to precipitate complement-mediated hemolysis. Anti-D has not been shown to have the ability to fix complement, with the exception of rare situations discussed elsewhere.[45] We therefore recommend that these events be termed AHR.

Identification of appropriate patients to receive RhIG

When a patient presents with ITP requiring treatment, and RhIG treatment is a consideration, care must be taken to rule out host factors, including history, physical examination, or laboratory abnormalities, which may predispose the patient to AHRs, DIC, and/or ARF. Previously identified risk factors (Table 2) should be included in the evaluation of the appropriateness of using RhIG. The panel

recommends that an alternative ITP medication be used in these clinical situations if practical. This is especially true for patients older than 65 with these existing conditions, who represented a large percentage of the anecdotal reports of severe reactions and have been shown to be at higher risk of severe complications (Fig. 3).

Monitoring

The black box warning recommends monitoring patients in a healthcare setting for 8 hours after administration of RhIG. While the vast majority of patients will remain asymptomatic, the time of onset of symptoms (hemoglobinemia/hemoglobinuria) was within 4 hours in all but 6% of patients who developed severe AHR within the recommended 8-hour monitoring period (Table 3). The few patients who develop severe, clinically significant IVH will manifest important clinical signs, such as gross hematuria, myalgias, abdominal/flank pain, and so forth, which are sufficiently dramatic to be unlikely to be ignored. As with any medication, proper counseling on specific signs and symptoms that warrant immediate medical attention should be provided to patients and families before administration. This information is helpful in considering that some patients may be monitored in the home setting for development of AHR. The panel recommends taking individual patient and medical environment factors (such as access to transportation, presence and reliability of a companion, and proximity to medical provider or hospital) into consideration when determining length and location of monitoring after RhIG administration.

TABLE 3. Time to onset of symptoms with events classified as IVH and AHR*

Time (hr)	Definite IVH	Other AHR cases	Total cases
0-2	24 (34)	47 (19)	71 (23)
2-4	11 (16)	24 (10)	35 (11)
4-6	2 (3)	8 (3)	10 (3)
6-8	4 (6)	8 (3)	12 (4)
0-8	*41 (59)*	*87 (36)*	*128 (41)*
8-12	2 (3)	4 (2)	6 (2)
<12	0 (0)	1 (0)	1 (0)
8-12	*2 (3)*	*5 (2)*	*7 (2)*
12-24	10 (14)	13 (5)	23 (7)
<24	0 (0)	4 (2)	4 (1)
12-24	*10 (14)*	*17 (7)*	*27 (9)*
24-48	6 (9)	38 (16)	44 (14)
48-72	6 (9)	18 (7)	24 (8)
>72	3 (4)	30 (12)	33 (11)
Unknown	2 (3)	47 (19)	49 (16)
Total	*70*	*242*	*312*

* Data are reported as number (%).

Baseline

Our recommendations include careful history and examination as well as screening labs to identify the presence of the most commonly identified predisposing factors. The recommended tests and rationale for each are summarized in Table 4. A complete blood count should be performed to ensure that no baseline anemia nor another hematologic condition exists. We recommend a direct antiglobulin test (DAT) and antibody screen to rule out baseline immune hemolysis and identify patients who may be at increased risk for brisk hemolysis due to the underlying presence of RBC antibodies. A reticulocyte count should be performed to identify increased RBC turnover. In addition, we recommend a chemistry panel including creatinine and blood urea nitrogen (BUN) to establish normal baseline renal function as well as liver function tests including bilirubin. Physical exam findings and history should not be suggestive of current or recent EBV or other significant infection. Importantly, less serious infusion-related adverse events can be lessened or eliminated with the routine use of premedications.

TABLE 4. Recommended baseline lab testing and monitoring

Test	Before treatment	After treatment (time)	Rationale
CBC	Yes	1-3 days after infusion if first administration	Evaluate for presence of baseline anemia, degree of hemolysis, and improvement in PLT count after treatment
Differential and PBS review	Yes	No	Evaluate for evidence of existing hemolysis, severe infection, other conditions
DAT and antibody screen	Yes	No (positive after treatment in almost all cases)	Patients with existing antibodies may be at increased risk of AHR
Reticulocyte	Yes	No	Baseline hemolysis
Urinalysis (dipstick only, unless positive for blood)	Yes	1-2 hr (dipstick; encourage fluids to facilitate)	Existing renal disease predisposes to ARF in the setting of AHR
Serum creatinine	Yes	Yes, only if posttreatment Hb decreased by >1 g/dL	Underlying renal disease predisposes to ARF in the setting of ARF
BUN	Yes	Yes, only if posttreatment Hb decreased by >1 g/dL	Existing renal disease predisposes to ARF

BUN = blood urea nitrogen; CBC = complete blood count.

After treatment

In addition to posttreatment testing recommended by the FDA,[22] follow-up contact with outpatients 1 to 2 days after treatment is another consideration, especially for patients with any factor placing them at increased risk for serious adverse events who receive anti-D as the best alternative.

CONCLUSIONS

RhIG remains an effective and approved primary treatment for thrombocytopenia due to ITP. Recent concerns about safety have not been based on novel data or an increased incidence of occurrence or severity than previously reported, but these serious adverse events remain important issues in the use of IV RhIG in the treatment of children and adults with ITP. "Signal detection" epidemiology studies have led to identification of a patient population at increased risk for severe complications as a result of treatment with this medication. Avoiding the use of RhIG in the relatively small number of patients at increased risk for AHR, DIC, and ARF should further reduce the incidence of these rare complications. Careful selection of the treatment population and posttherapy monitoring will allow for the early detection of problems and can ensure rapid institution of supportive therapies, such as high-dose IV corticosteroids and aggressive hydration to prevent or ameliorate negative outcomes. Currently available data suggest that the safety profile of RhIG may not be significantly different than that of other treatment options for patients with ITP such as IVIG.

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CONFLICT OF INTEREST

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