Use of Intravenous Anti-RhD Immunoglobulin (RhIG) in the Treatment of Primary Immune Thrombocytopenia

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ABSTRACT

Commercialized intravenous immunoglobulin (IVIG) products have been used since the early 1980s for various patient treatment options, specifically to induce an immunomodulatory and therapeutic effect. IVIG, a pooled immunoglobulin G (IgG) preparation, is used for patients with immune deficiencies, inflammatory conditions, and autoimmune disorders such as primary immune thrombocytopenia (ITP). Front-line therapies for ITP include corticosteroids, IVIG, or anti-RhD immune globulin (RhIG). WinRho SDF (Cangene Corporation, Winnipeg, Manitoba, Canada), a RhIG preparation, was FDA-approved for use in 2005 and is used for treatment of patients with ITP through what is called a Fc blockade mechanism. After intravenous WinRho administration, patient platelets are spared from clearance by the spleen and with a good response to treatment, the patient's platelet count increases. WinRho is not without potential side effects and also impacts the transfusion service pre-transfusion testing in the event that the patient undergoing treatment requires red cell transfusion. In 2010, a work group of experts reviewed the warnings associated with RhIG and concluded that assuming that patients are appropriate candidates for RhIG, monitored in a clinical setting for 8 hours after administration, RhIG products such as WinRho are considered a very effective front-line therapy for ITP.[1] Effective first line therapies can circumvent the necessity for less-desirable second line therapies such as an invasive splenectomy or life-long treatment with thrombopoietin-receptor agonists (TPO-RAs) to increase platelet counts.

ABBREVIATIONS: IVIG – intravenous immunoglobulin, ITP – primary immune thrombocytopenia, RhIG – Rh immune globulin, TPO-RAs – thrombopoietin-receptor agonists, MPV – mean platelet volume, RBC – red blood cell, HUS – hemolytic uremic syndrome, TTP – thrombotic thrombocytopenic purpura, DIC – disseminated intravascular coagulation, CBC – complete blood count, PT – prothrombin time, APTT – activated partial thromboplastin time, FDA – Food and Drug Administration

INDEX TERMS: Thrombocytopenia, Immunoglobulin G, Immunoglobulins, Intravenous; Receptor, Fc; Rho(D) Immune Globulin, Blood Transfusion

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INTRODUCTION

Immune thrombocytopenic purpura, now called primary immune thrombocytopenia (ITP), is a disease state in which IgG autoantibody production and attachment to platelets result in clearance of the antibody-coated platelets by reticuloendothelial cells, primarily in the spleen. The platelet surface glycoprotein sites that are targeted in the majority of ITP cases are glycoprotein GPIIb/IIIa, and/or GPIb/IX. In patients with ITP, the usual 7 to 10 day platelet lifespan can be reduced to mere hours, resulting in thrombocytopenia. ITP can present in either an acute or chronic form. There is a spectrum of symptoms, based on the severity of the disease. Very mild cases may be asymptomatic, more severe cases may involve epistaxis, mucocutaneous bleeding, and the most severe cases may result in bleeding such as gastrointestinal (GI) bleeding or intracranial hemorrhage due to a very low platelet count (<10,000/μL). The hallmarks surrounding diagnosis are isolated thrombocytopenia with associated purpura accompanied by enlargement of

the spleen, liver, and lymph nodes. Petechiae and purpura are common, but not observed in all cases. First line therapies, as recommended by 2010 International Consensus Guidelines, include corticosteroids, IVIG, and/or anti-D immune globulin (such as WinRho).[1] Since ITP involves immune destruction of platelets, which could also include transfused platelets, platelet transfusions are usually not considered unless the patient is bleeding or at very high risk of bleeding.

Acute ITP is more common in younger children, presents with a platelet count of <20,000/μL, often follows a viral illness, and usually resolves within 2-6 weeks with no treatment needed unless the platelet count is <10,000/μL and the child is at risk of spontaneous hemorrhage. On the other hand, chronic (>12 months' duration) ITP has a gradual onset, thrombocytopenia, and the disorder may persist for a much longer period of time during adulthood. With the extended persistence of the disease, there are cycles of remission and exacerbation. An international consensus report on the investigation and management of primary immune thrombocytopenia states that treatment is rarely indicated in patients with platelet counts above 50,000/μL.[2] On the other hand, if there are additional risk factors or if there is an immediate need to treat based on risk of hemorrhage, WinRho RhIG is considered a treatment of choice in these urgent situations.

LABORATORY RESULTS AND OBSERVATIONS

The hematology/coagulation laboratory testing profile for ITP patients usually encompasses only platelet abnormalities. Platelet counts are low and platelets are usually increased in size as noted by an increased mean platelet volume (MPV) result when using an automated hematology analyzer. While bone marrow evaluation is usually not indicated, megakaryocytic hyperplasia is usually seen in the bone marrow as the body is responding to this platelet destruction syndrome. Red blood cell (RBC) and leukocyte morphology is normal. The evaluation of the peripheral blood smear may be instrumental in helping confirm ITP as opposed to similar syndromes. For example, schistocytes on the smear would point towards hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP), whereas observation of inclusion bodies or excessive amounts of erratically sized (both small and large) platelets would rather point towards an inherited disease.

USE AND DOSING

For WinRho, the indications for use for ITP patients are: (1) RhD positive children with chronic or acute ITP, (2) RhD positive adults with chronic ITP, and (3) RhD positive children and adults with ITP secondary to HIV infection.[3] Other requirements to ensure the safety and efficacy of the anti-D intravenous administration for ITP patients are that the patient should have an adequate hemoglobin level (>10g/dL) and the patient must be non-splenectomized. If the patient's hemoglobin is less than 10g/dL, a smaller dose of WinRho should be given. When administered, WinRho will result in an increase in platelet counts within 1-2 days and peak within 7-14 days.[3] For this reason, it is a treatment of choice in urgent situations. WinRho has not proven to be useful in cases where patients have thrombocytopenia for reasons other than ITP, in RhD negative patients, and/or in patients who have been splenectomized.[3] The spleen is the necessary site to clear the antibody coated cells (whether that be immunoglobulin-bound red cells or platelets).
Recommended dosing is as follows and administration generally only takes 3-5 minutes.

- Initial Dosing: An initial dose of 250 international unit/kg (50 mcg/kg) body weight, given as a single injection is recommended for the treatment of ITP.[3]
- Subsequent Dosing: If subsequent therapy is required to elevate platelet counts, an intravenous dose of 125 to 300 international unit/kg (25 to 60 mcg/kg) body weight of WinRho SDF is recommended.[3] The frequency of dosing and the dose used in maintenance therapy should be determined by the patient's clinical response by assessing platelet counts, RBCs, hemoglobin, and reticulocyte levels.[3]

During clinical trials, efficacy was evaluated in four groups of patients, including childhood chronic ITP, childhood acute ITP, adult chronic ITP, and ITP secondary to HIV infection.[3] (Table 1). Efficacy was determined when expected platelet count response thresholds were met or exceeded.

Table 1. Clinical WinRho trials results of four patient groups.[3]

Patient group	Expected response threshold	Number of responders/number evaluated	% Efficacy
Chronic ITP – Child -Non-splenectomized -RhD positive -ITP duration > 6 months	Platelet increase to ≥ 50,000/μL and at least double the baseline	19/24	79%
Acute ITP – Child -Non-splenectomized -RhD positive -Platelet count <20,000/μL	Platelet increase ≥ 50,000/μL	32/38	84%
Chronic ITP – Adult -Non-splenectomized -RhD positive -ITP duration >6 months -Platelet count <20,000/μL	Platelet increase ≥ 20,000/μL	21/24	88%
ITP secondary to HIV – Adult or Child -Non-splenectomized -RhD positive -Platelet count ≤ 30,000/μL	Platelet increase ≥ 20,000/μL	57/63	90%

MECHANISM OF ACTION

As with RhoGam (Kedrion Biopharma, Inc.), the full mechanism by which WinRho works is not completely defined and understood. The mechanism by which a RhIG such as WinRho is postulated to work is referred to the Fc blockade effect. The IgG immunoglobulin in the WinRho preparation attaches to the patient's RhD positive red cells upon administration. At first thought, this may seem to be an odd approach, especially since the patient already has IgG antibody targeting and binding the platelets. However, with both RhD+ red cells now coated with WinRho and the patient's platelets bound with IgG autoantibody, the immunoglobulin-bound red cells are preferentially cleared by the macrophages in the spleen. (Figure 1). With this preferential clearance of the antibody bound red cells, more platelets are spared and the patient's platelet count rises and thus risk of spontaneous hemorrhage is decreased. However, since WinRho bound RBCs are now being cleared, there is a purposeful, slight RBC hemolysis that is induced. Pooled data from ITP clinical studies demonstrated a mean decrease from baseline in hemoglobin levels of 1.2 g/dL within 7 days after administration of WinRho.[3] Additionally, more recent reports have indicated that additional proposed therapeutic mechanisms of IVIG products include actual suppression of antibody production, cellular immunosuppression, and release of anti-inflammatory cytokines.[4]

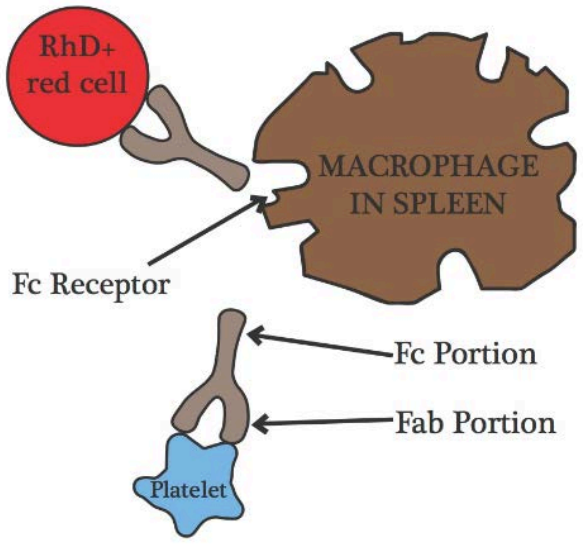

Figure 1: Fc Blockade Mechanism. RhIG-bound red cell and preferential binding to the macrophage via the Fc receptor site for subsequent red cell clearance and sparing of the IgG autoantibody-bound platelet.

SIDE EFFECTS AND RISKS

While slight hemolysis is expected with RhIG, a severe

side effect in some patients is accelerated red cell destruction, resulting in a more precipitous drop in the hemoglobin level. If a patient has a history of warm autoimmune hemolytic anemia and/or renal insufficiency, treatment with WinRho would be contraindicated. In a worst-case scenario post-administration, symptomatic anemia ensues, including acute respiratory distress. Because of this potential risk, within the 8 hours of WinRho administration, clinicians are recommended to closely monitor the patient for signs of accelerated hemolysis. This could include, but not limited to a dipstick urine test for hematuria, observing for physical symptoms such as back pain, chills, shaking, and/or fever, and/or blood tests to detect hemolysis such as plasma hemoglobin, haptoglobin, LDH, and direct and indirect bilirubin.[3] In severe cases, disseminated intravascular coagulation (DIC) may occur and tests such as the D-Dimer may be necessary in addition to a complete blood count (CBC), prothrombin time (PT) and activated partial thromboplastin time (APTT). WinRho is human plasma derived preparation and thus carries small risk of infectious disease transmission. This product undergoes donor screening and viral inactivation steps.

A Food and Drug Administration (FDA) mandated black box warning was issued in 2010 for all RhIG preparations related to causes of extravascular hemolysis.[5] However, despite risks that can be mitigated by close post-administration patient monitoring, if the patient is in a crisis with a dangerously low platelet count and meets the criteria for administration of WinRho, this type of RhIG therapy has become a very popular treatment due to the very quick response rate in elevating the platelet count. After the issuance of the FDA black box warning, 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.[5] The working group consensus was that RhIG has comparable safety and efficacy to other front-line agents for the treatment of ITP.[1] Safety is improved by careful patient selection and careful post-administration monitoring. Use of RhIG for ITP treatment has remained in widespread use with more than 225,000 estimated infusions since the first RhIG FDA approval in 1995.[5]

MANANGEMENT OF ACCELERATED RED CELL DESTRUCTION AND IMPACT TO THE TRANSFUSION SERVICE

Alternatively, if the patient's hemoglobin drops more than expected and the patient is symptomatic, it is possible that a specimen will be submitted to the transfusion service for ABO/Rh, antibody screen, and possible order for crossmatched red cell components. WinRho administration can present some unique challenges in the blood bank/transfusion service, yet a keen blood bank technologist can help streamline the serologic management of these cases. The usual testing profile, assuming that the patient has not recently formed unexpected red cell alloantibodies, would be a positive direct antiglobulin test (DAT) due to IgG, positive autocontrol (if performed), positive antibody screen, and a clear anti-D pattern when the patient's plasma or serum is tested against a red cell panel. If the technologist does not have a patient history (or is not seeking this key information), it may first be postulated that this patient possibly has an immune-related anti-D formation of unknown etiology. Drawing this conclusion and proceeding to refer the specimen to an immunohematology reference laboratory for further follow-up would be a premature decision if the patient's current disease state and medication administrations are not sought out and obtained. This is especially important now that WinRho is commonly used for ITP treatment and passively acquired anti-D would be expected when performing serologic testing. The immunohematologist should also be aware, albeit a rare occurrence, that IVIG/RhIG preparations may contain other atypical red cell antibodies and thus result in the detection of other passively acquired antibodies via pre-transfusion testing. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, C and E) and other blood group antibodies (for example Duffy and/or Kidd blood group system antibodies) may cause a positive direct and/or indirect antiglobulin test.[6] Passive transfer of anti-A and/or anti-B can cause an ABO reverse typing discrepancy.

On the other hand, if this transfusion service testing profile of anti-D in a RhD positive individual is observed for a patient with a diagnosis of ITP and the patient has recently received WinRho, the serologic picture is explained. However, other decisions need to be made in the event that the patient requires a red cell transfusion. Namely, transfuse crossmatch compatible

RhD negative units or give RhD positive, crossmatch incompatible units? At this point, the patient's physician and possibly the transfusion service medical director should be consulted. The physicians will likely need to weigh which situation is more severe, the patient's low platelet count or the patient's dropping hemoglobin. While the decision varies based on the patient's clinical presentation, it would make more sense to provide RhD negative crossmatch compatible red cells if the patient's oxygen carrying capacity is compromised and needs to be boosted quickly. That is, transfusing red cells the same Rh type as the patient (RhD positive) could exacerbate the situation when clear signs of more aggressive hemolysis are observed. Alternatively, if the platelet count is very low due to a state of aggressive ITP, transfusing RhD negative red cell components could theoretically reduce the efficacy of the WinRho, since the premise by which this product works is to bind to RhD positive cells. This scenario clearly emphasizes the importance of laboratorians having access to the patient's diagnosis and medication administration history along with ensuring that physician involvement is triggered if it is possible that a red cell transfusion is necessary while the patient is actively receiving the WinRho preparations to manage the ITP.

COMPARISON OF FIRST LINE THERAPIES

First line therapies usually include corticosteroids, IVIG, and/or anti-D IVIG such as WinRho. While preferences may vary by practitioner, there are several comparative reasons why an anti-D preparation such as WinRho may be the first line therapy of choice. While corticosteroids are inexpensive and generally attempted first, there can be a several-day platelet response phase and then platelet counts decrease immediately after therapy is discontinued. This is further complicated by an increased incidence of side effects if dosages and administration durations are extended.[7] While non-anti-D IVIG preparations can be used for the 15% of the population that is RhD negative and have been proven to be effective with a rapid platelet response, downsides include a >3 hour infusion time, higher infusion volume, possible toxicity, and cost. Side effects for IVIG, including hemolytic anemia, are very similar to WinRho.[8] Alternatively, anti-D IVIG such as WinRho is infused in a matter of a few minutes, the response is quick, and platelet response may also be related to dose.[8] Multiple studies have demonstrated that IV anti-D administered at 75 μg/kg, instead of 50 μg/kg dose, increases the overall platelet count comparable to that of IVIG.[2,5,9]

CONCLUSIONS

IV preparations such as RhIG (assuming that the patient is a proper candidate) are an effective alternative to IVIG, can be infused in a significantly shorter time and smaller dose, is produced from a significantly smaller donor pool, and has a potential longer platelet response.[1,5] Likewise, a prior cost study comparison showed that the cost of IVIG is approximately 70% higher than the cost of a dose of RhIG.[10] In conclusion, assuming that the patient is a proper candidate, utilizing RhIG preparations such a WinRho as opposed to IVIG should prove to have similar safety but improved comparative clinical efficacy in raising and maintaining platelet counts in patients with ITP. Due to the continued widespread use of RhIG treatment for ITP patients, laboratory staff, especially in the transfusion service, should be aware of the side effects and impact to pre-transfusion serologic testing.

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