

TRANSFUSION MEDICINE UPDATE



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Rh Immune Globulin: Formulations and Indications

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INTRODUCTION

Rh immune globulin (RhIG) is a concentrate of predominantly IgG anti-D derived from pooled human plasma. RhIG was originally developed in the early 1960's to prevent Rh hemolytic disease of the newborn in Rh negative mothers. Its use has expanded to include prevention of Rh immunization from transfusion and treatment of immune thrombocytopenic purpura (ITP).

DESCRIPTION

RhoGam™ is an **IM only** sterile solution containing 300 µg (1500 IU) of anti-D from pooled human plasma. A single dose is sufficient to suppress the immune response to up to 15ml of Rh positive red cells. The product undergoes two steps to prevent viral transmission: cold alcohol fractionation and nanofiltration. Although viral transmission risk is not completely eliminated, the safety profile for this preparation is excellent with no reported transmissions of HIV or hepatitis in the USA. There is a small amount of IgA, typically less than 15 µg per dose. The product is only approved for suppression of Rh immunization. This preparation is not approved for the treatment of ITP.

Win Rho SDF™ is a sterile, freeze-dried RhIG preparation of anti-D from pooled human plasma, which can be given **IV or IM**. It was developed for the treatment of ITP and is available in doses of 120 µg (600 IU), 300 µg (1,500 IU) or 1,000 µg (5,000 IU) in 1.25 to 8.5 ml of sterile 0.9% NaCl, depending on the dose and route of administration. The product also contains a small amount of IgA – approximately 5 µg/ml. The product is prepared by chromatographic extraction, followed by two steps to prevent viral transmission: nanofiltration to remove non-enveloped viruses and solvent-detergent treatment to inactivate lipid enveloped viruses. Although viral transmission risk is not entirely eliminated, the safety profile for this preparation is also excellent. The 300 µg vial contains sufficient anti-D to suppress the immune response to 17 ml or less of Rh positive red cells. Only the IV form can be used for the treatment of

ITP. The product is also approved for suppression of Rh immunization.

Rhophylac® is a newly FDA approved, sterile RhIG solution of anti-D from pooled human plasma which can be given **IV or IM**. A single dose contains 300 µg (1500 IU) of anti-D in 2 ml of solution and is sufficient to suppress the immune response to up to 15ml of Rh positive red cells. The product also contains a small amount of IgA, less than 5 µg/ml. It is prepared in the same manner as WinRho SDF™ - chromatographic extraction, followed by two steps to prevent viral transmission: nanofiltration to remove non-enveloped viruses and solvent-detergent treatment to inactivate lipid enveloped viruses. The product is only approved for suppression of Rh immunization. This preparation is not approved for the treatment of ITP.

INDICATIONS AND DOSAGE

Routine antenatal prophylaxis for prevention of Rh immunization in Rh negative women at 28-30 weeks of gestation. This dose prevents the 1-2% risk of Rh immunization that can occur after week 28. When combined with a dose at delivery, the risk of Rh immunization is reduced to 0.1%. RhIG is not indicated in women already immunized with anti-D. The recommended dose is 300 µg IM (any of the preparations) or 300ug IV (WinRho SDF™ or Rophylac®).

Post partum prophylaxis for prevention of Rh immunization in Rh negative women with an Rh positive neonate. The dose should be given within 72 hours of delivery, but should not be withheld if more than 72 hours have elapsed. A rosette test and, if needed, a Kleihauer-Betke test is done to determine whether more than 1 vial of RhIG is needed. Only rarely (0.3%) does a fetal maternal hemorrhage exceed the neutralization capacity of one vial. Thus in >99% of cases the following doses are recommended: RhoGAM™ 300 µg IM, Rhophylac® 300 µg IM or IV, or WinRho SDF™ 120 µg IM or IV.

Obstetric conditions/complications

Pregnant Rh negative women are candidates for RhIG if they experience the following complications: miscarriage, abortion, threatened abortion, ectopic pregnancy, placental hemorrhage or undergo an invasive procedure including: amniocentesis, chorionic villus sampling, external version or abdominal trauma. If these events occur in the first trimester a reduced dose of RhIG (e.g. MICRhoGAM®) could be used. However, a full dose is typically given due to uncertainty regarding calculating the length of gestation or inadvertently using a reduced dose when a full dose is required.

Preventing Rh immunization in an Rh negative recipient of an Rh positive cellular blood component (eg platelets or packed red cells)

As little as 100 µl of Rh positive red cells is sufficient to stimulate anti-D in an Rh negative recipient. For women of child bearing age or children, Rh immunization may place them at future risk of pregnancy complicated by hemolytic disease of the newborn. In male children, life long anti-D may develop and complicate future transfusions. These patients, therefore, should be evaluated as candidates for RhIG immune prophylaxis. When evaluating such patients, the underlying disease should be considered. Whereas 75-85% of normal Rh negative individuals will make an anti-D when exposed to Rh positive blood components, the response is much lower in patients. Rh negative cancer patients transfused with Rh positive platelets have been reported to make anti-D in <5% of cases. Treatment should be given within 72 hours of transfusion, but should not be withheld if more than 72 hours have elapsed. A 300 µg dose neutralizes 15 ml (RhoGAM™ or Rhophylac®) or 17ml (WinRho SDF™) of transfused Rh positive red cells. For calculation purposes, a whole blood platelet unit is estimated to contain no more than 0.5 ml of red cells. An apheresis platelet concentrate contains no more than 2 ml of red cells. Thus, a single 300 µg dose is more than sufficient to prevent Rh immunization to the red cells in a single dose of platelets. If an entire Rh positive red cell unit is transfused (contains approximately 200 ml of red cells), then the requirement for multiple RhIG vials and the risk of complications due to hemolysis of the transfused Rh positive cells must be weighed against the risk and consequences of Rh immunization.

Immune Thrombocytopenic Purpura (ITP)

The only RhIG preparation which has been approved for the treatment of ITP is IV WinRho SDF™. It is approved in non-splenectomized, Rh positive patients including: children with acute or chronic ITP, adults with chronic ITP, or children or adults with ITP secondary to HIV infection, who require an increase in platelet count to prevent excessive hemorrhage.

The passively administered anti-D coats the patient's red cells, inducing extravascular hemolysis in the spleen, thereby inhibiting the removal of platelets. The initial dose of IV WinRho SDF™ is 50 µg/kg (250 IU/kg) body weight given as a single injection or two divided doses over two days. If the patient has a hemoglobin level <10g/dl, a reduced dose of 25-40 µg/kg should be used to minimize the risk of severe anemia. If subsequent therapy is required to raise the platelet count, a dose of 25-60 µg/kg body weight is recommended. The response rate, defined as an increase in platelet count >20,000/µl, is reported to be 85-90%.

ADVERSE REACTIONS

IM injection may cause pain at the injection site. Occasional symptoms reported with IM or IV RhIG administration include: transient fever, malaise, hives, headache and/or chills. More rarely, nausea, vomiting, hypotension, tachycardia, wheezing, chest tightness, and allergic or anaphylactic type reactions have been reported. In patients receiving Win Rho SDF™ for ITP, a drop in hemoglobin is expected and averages 1.7g/dl. A small proportion (3.7%) of patients have an exaggerated hemolytic response and experience a drop of 4-6 g/dl. Rarely (4 cases), intravascular hemolysis and death have occurred.

References

- RhoGAM™ package insert, 9/2001.
- Win Rho SDF™ package insert, 1/20/2000.
- Rophylac® package insert, 1/2004.
- Andrew, M et al. A multicenter study of the treatment of childhood chronic ITP with anti-D. J Peds 1992;120:522-7.
- Bussell JB et al. intravenous anti-D treatment of ITP: Analysis of efficacy, toxicity and mechanism of effect. Blood 1991;77:1884-93.

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