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The Role of Anti-D in the Management of Chronic and Secondary Forms of ITP

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BACKGROUND

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by a low platelet count and mucocutaneous bleeding. The estimated incidence is 100 cases per 1 million persons per year, and about half of these cases occur in children. Immune thrombocytopenic purpura is classified as primary or as secondary to an underlying disorder and as acute (of six months or less in duration) or chronic. Adult-onset and childhood-onset immune thrombocytopenic purpura are strikingly different. In more than 70 percent of children, the illness resolves within six months, irrespective of whether they receive therapy. By contrast, immune thrombocytopenic purpura in adults is generally chronic, the onset is often insidious, and approximately twice as many women as men are affected[5]. Secondary forms of ITP occur in association with the following conditions:

- Disorders of the immune system such as systemic lupus erythematosus, antiphospholipid syndrome and immunodeficiency states such as IgA deficiency and common variable hypogammaglobulinemia
- Lymphoproliferative disorders such as chronic lymphocytic leukemia, large granular lymphocytic leukemia and lymphoma.
- Infections such as human immunodeficiency virus (HIV), hepatitis C (HCV) and dengue hemorrhagic fever. There are many other infectious diseases that are associated with thrombocytopenia but the immunologic basis for the thrombocytopenia in these other infections has not been established. For this discussion, we will focus on HIV and dengue secondary ITP where some data are available
- Drug induced commonly after heparin administration and use of quinidine.

The treatment of ITP since the 1920's consisted of splenectomy until cortisol was discovered in 1948 and prednisone shortly after. In 1951, the young hematologist in training, Dr. William Harrington, infused himself with plasma from a patient with immune thrombocytopenic purpura. He rapidly developed severe, but transient, thrombocytopenia and was at risk for serious hemorrhage. Thus, the humoral autoimmune cause of ITP was established[1]. In 1981, Paul Imbach demonstrated that ITP patients treated with high doses of intravenous immune globulin (IVIG) manifested a rapid increase in platelet counts to safe hemostatic levels[2]. In these studies, 13 children received 0.4 g of IgG per kg body weight per day on 5 consecutive days. The platelet counts began to rise within 24-48 hours in all patients[3]. In 1983, Salama developed the hypothesis that the mechanism of action of IVIG in ITP may be due to competitive inhibition of the reticulo-endothelial system function by sequestration of the patients' red blood cells. This hypothesis was supported by the findings that IVIG treatment induces a clinically inapparent hemolysis as evidenced by a decrease in haptoglobin levels[4].

Cangene Corporation, (Winnipeg, Manitoba. Canada) undertook studies from 1987-1989 to evaluate the efficacy and safety of the use of its anti-D immune globulin (WinRho® SDF).

WinRho® SDF became the first anti-D immune globulin to be licensed for the treatment of ITP with marketing authorization received by the FDA in 1995, Health Canada in 1996 and DCGI in 1997.

PRODUCT DESCRIPTION

WinRho® SDF *is an Anti-D (Rh_0-D) Immune Globulin* (WinRho® SDF) is a sterile freeze dried gamma globulin (IgG) fraction of human plasma containing antibodies

to Rh_0 (D), prepared by Cangene Corporation (Winnipeg, Canada) by an anion-exchange column chromatographic method. The product potency is expressed in international units by comparison to the World Health Organization (WHO) standard. The conversion of "µg" to "IU" is 1µg = 5 IU. WinRho® SDF is licensed for the treatment of Immune Thrombocytopenic Purpura (ITP) in India. For ITP treatments, the intravenous route is preferred as intramuscular administration of large volumes of immune globulin may lead to painful and potentially life threatening hematoma formation in this population with hemorrhagic symptoms. WinRho® SDF is formulated for intravenous administration (ITP) and for intramuscular administration (prevention of Rh sensitization).

Win Rho SDF ITP STUDIES

Results of pivotal studies for chronic ITP and ITP secondary to HIV infection are presented with a brief description of the study design and the statistical analyses of these data. Data from an interim analysis of 2 randomized placebo controlled studies in thrombocytopenic adults and children with dengue hemorrhagic fever are presented. In addition, a summary of a systematic review of the literature (SRL) that compared IVIG and anti-D in ITP patients is provided in order to provide a general risk and benefit comparison to a similar front line treatment.

Efficacy Endpoints

In most ITP trials and publications, the efficacy of ITP treatments is typically defined as an increase in platelet count by 20,000 per cubic mm above the baseline platelet level or an increase in platelet count >50,000 per cubic mm. It is recognized that this represents a surrogate marker of efficacy, since measurements of efficacy with bleeding scores and/or clinical outcome such as decrease in intracranial hemorrhage are impractical.

In patients with chronic ITP or those with ITP secondary to HIV infection, the goal of therapy is to raise the platelet count to a "safe threshold" and maintain the platelet count above the threshold for as long as possible, thereby reducing the risk of a catastrophic hemorrhage. There is debate about what platelet count is considered a "safe threshold". Generally, if the platelet count is ≥50,000/cubic mm the patient is at a lower risk of sustaining a life threatening hemorrhage. Duration of effect and time to re-treatment may be more clinically important measures of efficacy in chronic ITP than time to platelet response since they reflect the frequency that treatments are administered.

On the other hand, patients with acute ITP or dengue hemorrhagic fever patients with very low platelets may require rapid platelet rises to minimize the risk of hemorrhage. As such, the most important measure of efficacy with acute ITP and ITP associated with DHF may be response at 24 hours since it is imperative to raise the platelet count quickly to prevent life-threatening hemorrhages.

RESULTS

Table 1 summarizes the overall efficacy data set for anti-D (WinRho® SDF) from two sources, pivotal clinical studies and from the SRL. This serves as background information for efficacy measurements in the populations of interest in this review. It is demonstrated that the overall response rate in pivotal studies with WinRho® SDF is 87% (n=161) and with IVIG is 92% (n= 69) and this is comparable to the data obtained from the SRL wherein the overall response rate with WinRho® SDF was 80% (n=725) and IVIG was 86% (n=1918). WinRho® SDF appears to have a more sustained duration of effect (6.5-7.8 weeks) compared to the IVIG arm of the SRL (4.7 weeks). Although these findings are not statistically significant, this does suggest a longer time between re-treatments with WinRho® SDF.

Chronic Immune Thrombocytopenic Purpura in Adult

Table 2 presents the data from an open label conducted in 24 adults with chronic ITP who received

Table 1: Overall responses WinRho® SDF compared to IVIG

	Cangene studies		*Systematic review of literature*	
Efficacy Parameters	*WinRho® SDF*	*IVIG*	*WinRho® SDF*	*IVIG*
Number of Patients	161	69	725	1918
Overall Response (%)	87	92	80	86
Response within 24 Hours (%)	n/a	n/a	50	51
Response within 7 Days (%)	n/a	n/a	79	88
Mean Time to Response (days)	n/a	n/a	3.2	3.1
Mean Duration of Response (weeks)	7.8	n/a	6.5	4.7
Mean Peak Platelet Count (× 10^9/L)	165	346	202	183

multiple courses of treatment with WinRho® SDF, however, only efficacy outcomes for the two initial courses of therapy are presented along with the overall response rates. The overall response rate in this population was excellent with 88% of subjects responding to a mean dose of 46 µg/kg anti-D (p=0.0001). The mean duration of response in this population was also excellent. In Table 3 these efficacy endpoints are compared to comparable data from the SRL in which both adults and children with chronic ITP are included. When both adult and children populations are included in the anti-D pivotal studies the overall response rates is 90% with a mean duration of response of 8.9 weeks. This compares favorably with the mean duration of response of 7.9 weeks for WinRho® SDF and 5.1 weeks for IVIG suggesting a longer duration of effect for anti-D.

ITP Secondary to HIV Infection

Table 4 presents the results of an open label study conducted in 59 adults and children with ITP secondary to HIV infection where a mean dose of 49 µg/kg was used over multiple courses of therapy. The overall response rate in this population was 90% (p=0.0001) and the mean duration of response was 48.9 days. These data are not available for IVIG as the systematic review of the literature revealed few publications reporting efficacy or safety endpoints with IVIG in this population.

ITP Secondary to Dengue Infection

Two randomized placebo controlled pilot studies were undertaken in patients who exhibited secondary dengue infection. The goal of the studies was to determine:

- If the thrombocytopenia associated with dengue responds to anti-D.
- Which study populations [adults or children, and, severe thrombocytopenia (<50,000 platelet count) or moderate thrombocytopenia (50,000-100,000 platelet counts)] would best illustrate a response to anti-D immunotherapy.

Table 2: Response in adults with chronic ITP

Therapy	*Responders*	*Peak Platelet Count (× 10^9/L)*	*Maximum Change in Platelet Count from Baseline (× 10^9/L)*		*Duration of Response (days)*
	n/N (%)	*Mean (range)*	*Mean*	*P-value[1]*	*Mean (range)*
First course	20/24 (83)	92.6 (8-210)	66.7	0.0001	115.7 (2-1033)
Second course	10/13 (77)	100.7 (19-252)	69.5	0.0023	59.3 (14-165)
Overall	21/24 (88)	92.3 (8-229)	65.6	0.0001	89.6 (2-599)

n: Number of responders; N: Number of assessable patients, [1] P-value calculated by paired t-tests

Table 3: Responses in chronic ITP

Efficacy Parameter	***Chronic ITP***			
	Cangene Studies		*Systematic Review of Literature*	
	WinRho® SDF	*IVIG*	*WinRho® SDF*	*IVIG*
# Patients	51	0	287	349
Overall Response (%) of patients	90	n/a	75	87
Response within 7 days (% of patients)	n/a	n/a	86	85
Mean Duration of Response (weeks)	8.9	n/a	7.9	5.1
Mean Peak Platelet Count (× 10^9/L)	**159**	**n/a**	**114**	**189**

Table 4: Responses in adults and children with HIV infection

Therapy	*Responders*	*Peak Platelet Count (x 10^9/L)*	*Maximum Change in Platelet Count from Baseline (x 10^9/L)*		*Duration of Response (days)*
	n/N (%)	*Mean (range)*	*Mean*	*P-value[1]*	*Mean (range)*
First course	44/59 (75)	87.3 (16-593)	66.6	0.0001	54.5 (4-724)
Second course	31/44 (71)	60.7 (9-201)	37.4	0.0001	40.2(10-159)
Overall	57/63 (90)	81.7 (16-593)	60.9	0.0001	48.9 (4-298)

n: number of responders; N: Number of assessable patients [1] P-value calculated by paired t-tests

Table 5: Responses in adults and children with dengue hemorrhagic fever

	Children < 50,000 Platelets		***Adults < 50,000 Platelets***		***Combined Studies < 50,000 Platelets***	
Criteria	*WinRho® SDF*	*Placebo*	*WinRho® SDF*	*Placebo*	*WinRho® SDF*	*Placebo*
Number	5	5	7	7	12	12
Mean Maximum Platelets at 48 hrs. (range)	**105,200** (27,408-182,992)	**72,800** (31,709-113,891)	**81,714** (0-163,432)	**66,857** (43,758-89,956)	**91,500** (42-978-140,022)	**69,333** (51,958-86,709)
Proportion of Responders (CI)	80% (28%, 99%)	40% (5%, 85%)	71% (29%, 96%)	71% (29%, 96%)	75% (43%, 95%)	58% (28%, 85%)
Mean Time to ↑ Platelets by 20,000 from Baseline	**36 hours (14, 58)**	**62 hours (28, 96)**	**43 hours (30, 57)**	**40 hours (19, 61)**	**40 hours (31, 49)**	**50 (33, 67)**

An interim analysis of the study results was planned and conducted at the end of the dengue season in the Philippines (November 2004) in order to calculate the progress of the study. Our findings, although not intended to be statistically powered are presented in Table 5 and Fig. 1.

There is a trend to higher platelet levels at 24 hours in children with severe thrombocytopenia who were treated with WinRho® SDF. This trend persists and by 48 hours the mean maximum platelet counts in WinRho® SDF treated children was 105,200 compared to 72,800 in placebo arm. Response was defined in this study as an increase of platelet count by 20,000/cu mm at 48 hours and the proportion of responders in the WinRho® SDF arm was 80% compared to 40% in the placebo arm. An unexplained observation in these studies is that this was not observed in adults with severe thrombocytopenia (Fig. 2). When the data from severely thrombocytopenic adults was combined with the data from children with severe thrombocytopenia (Fig. 3) the trend to higher platelet counts in WinRho® SDF vs. placebo treated patients was preserved (mean maximum platelet count 91,500 vs. 69,333 and proportion of responders 75% vs. 58% and mean time to increase platelet count by 20,000 from baseline 40 vs. 50 hours)[6].

CONCLUSION

The efficacy of Anti-D (WinRho® SDF) therapy of chronic ITP (88% response rate) and ITP secondary to HIV infection (90% response rate) is established and comparable to the efficacy of IVIG (87 % response rate). The labeling of WinRho® SDF for the treatment of ITP specifies that the product must be administered by the intravenous route for this indication and a total dose can be given by bolus over 5 to 20 seconds. Many clinicians prefer to dilute the product with intravenous solutions such as D-5-W or normal saline and administer the total dose over 20 to 30 minutes. This compares

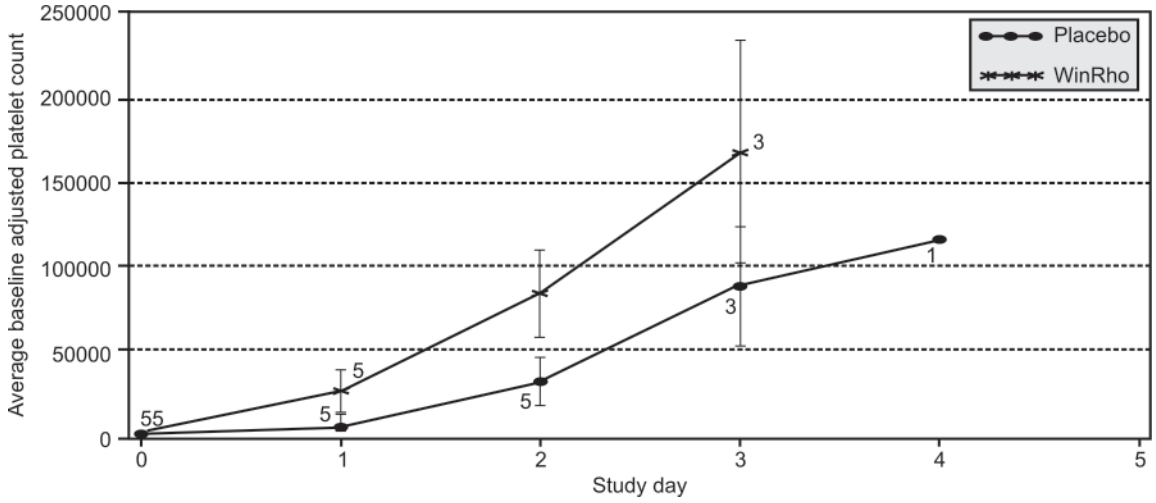

Fig. 1: Response in children with severe thrombocytopenia

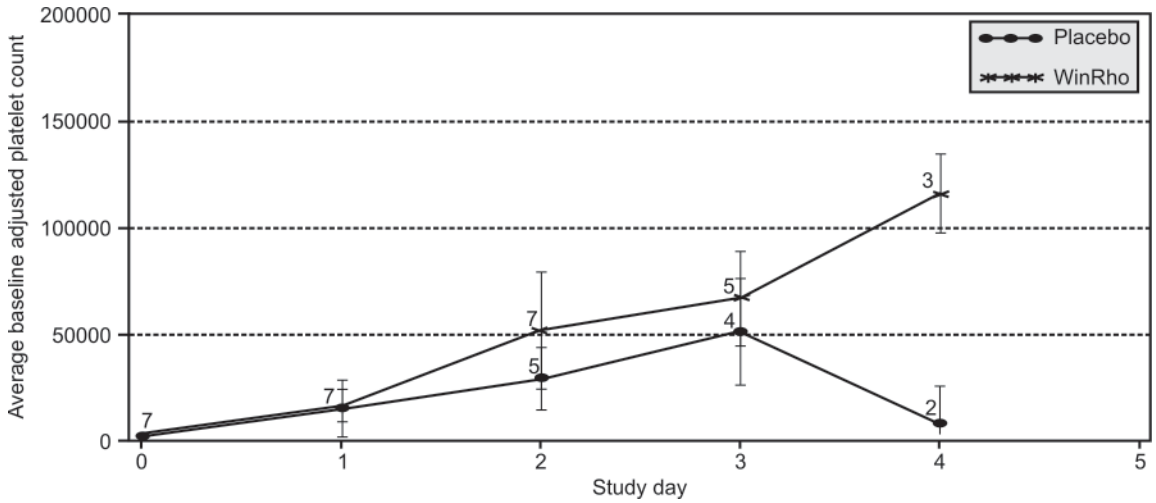

Fig. 2: Response in adults with severe thrombocytopenia

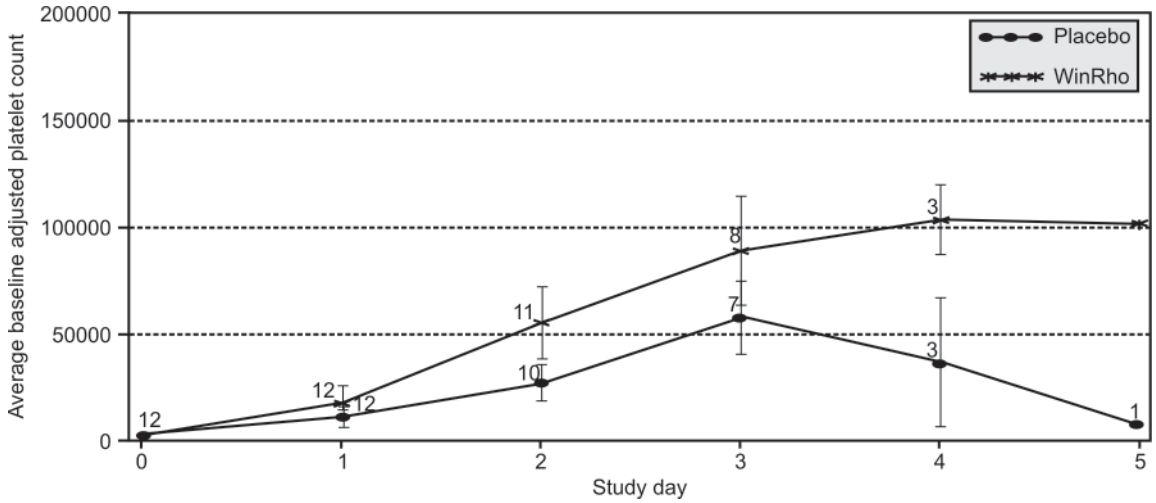

Fig. 3: Overall response (Adults and Children) with severe thrombocytopenia

favorably to the administration time of IVIG which is over several hours, sometimes over a 2 day period in order to administer a full dose. The systematic review of the literature allows for verification of the efficacy of anti-D in the populations examined and presents robust comparison data with IVIG. In addition the SRL presents the first published data suggesting that WinRho® SDF may have a longer duration of effect than IVIG although these findings must be verified in additional studies.

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