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Trends in anti-D immune globulin for childhood immune thrombocytopenia: Usage, response rates, and adverse effects

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Abstract

In 2010, the Food and Drug Administration (FDA) added a black box warning to anti-D immune globulin (Rho(D) immune globulin, anti-D) for immune thrombocytopenia (ITP) to warn of the complications related to severe hemolysis. The objective of this retrospective medical record review was to examine recent trends in anti-D use to treat ITP and rates of adverse events in a single large pediatric hematology program. Over a 7-year period, 176 (35%) of 502 ITP patients at our center received anti-D. Anti-D was the second most commonly prescribed drug for ITP from 2003 to 2010 overall and was given first most frequently (41%). Sixty-four percent of patients responded to anti-D, but 36% had adverse effects, including five patients requiring hospitalization. From 2003 to 2010, the use of anti-D as an initial therapy for ITP significantly decreased ($P < 0.001$). This trend preceded the 2010 FDA black box warning. In our experience, anti-D was associated with a significant number of adverse effects when used as a treatment for ITP, although none were life-threatening. Despite recent guidelines suggesting anti-D therapy for initial treatment for ITP, anti-D therapy for ITP has significantly decreased over the past 7 years.

Anti-D was licensed in 1995 by the FDA as a therapeutic option for ITP. Initially, it was a popular choice in ITP therapy, due to its rapidity of infusion and subsequent platelet response [1,2]. Anti-D coats Rh-positive red blood cells allowing competitive inhibition of the Fc receptors on splenic macrophages in the mononuclear phagocytic system [3,4]. Thus, some degree of hemolysis is an expected side effect. In initial trials, fevers, chills, and headaches were the most frequently reported adverse effect of anti-D and occurred in 2–3% of patients [2,5,6]. Hemolysis was variable, and hemoglobin decreased by an average of 1.7 g/dL (range 0.4–6.1 g/dL) [2]. In 1998, the manufacturer reported seven cases of acute-onset hemoglobinuria, one of which required dialysis [5,7]. Over the next 10 years, additional complications were reported, some of which resulted in fatalities.

In 2010, an FDA black box warning was added to anti-D for ITP to warn of the complications related to severe hemolysis, a historically well known potential side effect [8]. The 2011 American Society of Hematology pediatric guidelines suggest anti-D globulin as a first-line treatment in Rh-positive, nonsplenectomized children, supported by grade 2B evidence [9]. In keeping with the FDA warning, these guidelines recommend against using

anti-D in children with anemia due to bleeding or autoimmune hemolysis [9]. The objective of this study was to examine trends in anti-D use to treat ITP in a large pediatric population over the past 7 years and rates of adverse events.

We identified 502 subjects with ITP with a first visit to Children's Hospital Boston from April 2003 through June 2010. 68.7% (345) of patients in this ITP cohort received pharmacologic treatment. Of the 502 subjects, 176 (35%) received anti-D. Table I compares the characteristics of these patients with those who were not treated with anti-D. Those treated with anti-D were less likely to have secondary ITP (2.8% versus 10.8%, $P < 0.01$). In addition, patients treated with anti-D were more likely to have a lower platelet count at diagnosis (median platelet count 12,000 vs. 17,000 cells/uL, $P < 0.01$). Those patients treated with anti-D were more likely to have experienced a higher severity grade of their worst documented hemorrhage at any point during their diagnosis with ITP ($P < 0.01$). In general, patients treated with anti-D tended to be of similar age, gender, and race as those who did not receive anti-D. Forty-seven percent (176/371) of Rh-positive ITP patients received anti-D.

The most common indications for receiving anti-D were thrombocytopenia (58%), bruising (41%), and wet purpura (20%). Of those treated with anti-D, the subjects were ultimately diagnosed with newly diagnosed ITP (<3 months) in 49.7%, persistent ITP (3–12 months) in 17.2%, and chronic ITP (>12 months) in 33.1%. Ninety-five percent of patients treated with anti-D received a dose of 50 µg/kg. Anti-D was the second most commonly prescribed drug for ITP from 2003 to 2010. However, when treatments were ranked by order, anti-D was given first most frequently (41%). From 2003 to 2010, the use of anti-D as an initial therapy for ITP significantly decreased ($P < 0.001$) (Fig. 1). During the same time period, the use of steroids as initial therapy significantly increased ($P < 0.001$). There was no significant trend in use of IVIG or observation as initial therapy over time.

Among all patients who received anti-D, 43.6% were complete responders, 20.8% were partial responders, and 35.6% did not respond. None of the partial responders were categorized as a partial response due to bleeding after treatment. The median best recorded platelet count within 1 month of receiving anti-D was 90,500 cells/uL (IQR 28,000, 189,000 cells/uL). Of those with a complete or partial response to anti-D, the median duration of response was 3 weeks (IQR 2, 4 weeks). Multiple doses of anti-D were received by 48/176 (27.3%) patients with a range of 2–11 doses.

Of the 176 patients who received anti-D, 112 (36%) experienced adverse effects. The most common side effects were flu-like symptoms, nausea, and hemolysis (Table II). None of the patients experienced renal failure. Re-administration of the drug was not performed in 7% (13/176) of the patients, despite persistent ITP, because the side effects were intolerable. Severe hemolysis and flu-like symptoms occurred with the first infusion in 9/13 (69%) patients.

2.8% (5/176) of those who received anti-D required hospitalization due to complications of therapy. Indications for hospitalization included severe hemolysis in four of the patients and post-infusion observation in one patient due to flu-like symptoms. Two of the four patients with severe hemolysis required red cell transfusions. These more serious effects may have led to the decrease in anti-D use from 2003 to 2010 at our center. This decrease parallels the increase in steroid use (Fig. 1). Since no change was seen in the observation approach or use of IVIG, the increase in steroid treatment may be due to more restricted use of anti-D.

At our center, the majority of children who received anti-D over the last 7 years were treated due thrombocytopenia and bruising. Given the side effects of anti-D therapy, the risks and benefits of treating children with ITP who are not bleeding must be carefully considered.

Despite previous adverse events and the 2010 FDA black box warning, our center continues to use anti-D in ITP patients in whom it was successful prior to the boxed warning and as a third line agent in select patients refractory or intolerant to steroids and IVIG. In these patients, our center informs patients and parents of the FDA warning and uses less conservative monitoring than those suggested by the FDA.

Methods

All patients diagnosed with ITP, with a first visit to Children's Hospital Boston between April 2003 and June 2010, were eligible for this chart review. The 502 subjects with ITP, as previously described, were identified from hematology department records and from the following hospital wide ICD-9 billing codes: ICD9 287.3 (primary thrombocytopenia), 287.31 (immune thrombocytopenia purpura), and 287.32 (Evans syndrome) [11]. Demographic, laboratory, and treatment data were collected through a retrospective chart review. The study protocol was approved by the Institutional Review Board at Children's Hospital Boston.

Treatment responses were defined using the criteria recently proposed by an international working group [12]. Complete responders are defined as post-treatment count $>100,000/\mu\text{L}$ and no clinically relevant bleeding. Partial response is defined as post-treatment platelet count $30\text{--}100,000/\mu\text{L}$ and doubling of the baseline platelet count and no clinically relevant bleeding. "No response" is post-treatment platelet count $<30,000/\mu\text{L}$ or less a doubling of baseline platelet count or clinically relevant bleeding. "Clinically relevant bleeding" was defined as a Grade III bleed or higher [10]. Duration of response was only recorded in patients with follow-up platelet counts. Thrombocytopenia as an indication for treatment was defined by the physician, not a specific platelet count. Study data were collected and managed using REDCap electronic data capture tools developed by Vanderbilt University and hosted at Children's Hospital Boston [13]. Initial analysis compared the subset of patients who received anti-D with those who did not, using Chi-Square test or the Wilcoxon rank sum test. The Cochran Armitage test was performed to examine trends. Trends in treatments used patients who received therapy as a denominator and excluded those who were observed without treatment. Data were analyzed using SAS 9.2. All *P*-values are two-sided, and no adjustments have been made for multiple comparisons.

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Figure 1.

Trend in decreased anti-D globulin use ($P < 0.001$) and increased steroid use ($P < 0.001$) as initial therapies to treat ITP from 2003 to 2009. No trend in IV immunoglobulin use as initial therapy.

TABLE I

Comparison of the Clinical and Laboratory Characteristics of 502 Patients Diagnosed with ITP by Whether Patients Were Treated with Anti-D Globulin.

	No anti-D (N = 326)	Anti-D treated (N = 176)	P value
Median age at diagnosis (years)	6.5 (IQR 2.3, 13.3)	5.0 (IQR 2.2, 11.6)	0.06
Gender			0.22
Male	164 (50.3%)	78 (44.3%)	
Race			0.37
Caucasian	60.9%	63.6%	
Black	6.2%	6.3%	
Asian	2.8%	3.4%	
Unknown	30.1%	26.7%	
Median platelet count at diagnosis (kcells/uL)	17 (IQR 7, 40)	12 (IQR 4, 13)	<0.01
Median lowest documented platelet count (kcells/uL)	11 (IQR 5,27)	5 (IQR 3,8)	<0.01
Primary ITP	89.2%	97.2%	<0.01
Secondary ITP	10.8%	2.8%	
Worst Documented			<0.01
Bleeding ^a			
Grade 3	44.2%	60.2%	

^aBy Buchanan and Adix Bleeding Score [10]. No patients had fatal bleeds.

IQR = interquartile range

TABLE II

Adverse Effects in 176 Anti-D Globulin Treated ITP Patients

Adverse effects	N (%)
None	112 (63.6%)
Moderate–severe hemolysis ^a	31 (17.6%)
Infusion related illness (fevers/chills)	28 (15.9%)
Nausea	20 (11.4%)
Pain	7 (4.0%)
Renal failure	0 (0.0%)
Other/Unknown	6 (3.4%)

^aHemoglobin decrease below the normal range for age.