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Do the Acute Platelet Responses of Patients With Immune Thrombocytopenic Purpura (ITP) to IV Anti-D and to IV Gammaglobulin Predict Response to Subsequent Splenectomy?

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The acute platelet response to Intravenous Gammaglobulin (IVIG) has been reported to predict response to subsequent splenectomy of patients with ITP. The current study was undertaken to determine if the platelet response to IV anti-D (Winrho-SDF) predicts response to subsequent splenectomy. The 61 HIV-uninfected children and adults in this study had taken part in the pre-licensing studies of IV anti-D and were all those who not only had evaluable platelet responses to IV anti-D but also had undergone splenectomy *and* had information available describing its 1-year outcome. Results of treatment with IVIG were available in 38 of these 61 patients. Neither response to the initial infusion of IV anti-D, nor response to the initial or last IVIG, predicted the response in either children or adults to subsequent splenectomy. However, response to the *last* anti-D infusion in adults was strongly correlated ($P = 0.003$) to response to subsequent splenectomy as was hemolysis ≥2.0 gm/dl after IV anti-D ($P = 0.03$). There was no overall relationship between response to IV anti-D or IVIG, and response to subsequent splenectomy. However, a good platelet response in adults to the last IV anti-D and a hemoglobin decrease ≥2.0 gm/dl both appeared to predict response to subsequent splenectomy. Am. J. Hematol. 67:27–33, 2001.

Key words: ITP; thrombocytopenia; Rho(D); IV gammaglobulin; splenectomy; spleen; autoimmunity; bleeding

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an autoimmune disease resulting in often marked thrombocytopenia as a consequence of autoantibodies directed against platelets [1–4]. The clinical consequence of the thrombocytopenia is mucocutaneous hemorrhage which is infrequently severe. Splenectomy remains the only treatment that is curative in the majority of patients with ITP, although long-term followup is limited in the reports [5–8].

Intravenous infusions of gammaglobulin (IVIG) [9–11] and subsequently IV anti-D [12–14] have been used to increase the platelet count in patients with ITP since 1981 and 1983, respectively. The mechanism underlying the acute platelet responses of both these treatments appears to be Fc receptor blockade [11,15–17], and both have been referred to as "medical splenectomies". IVIG has been shown to be effective in patients of any blood type and in those who have undergone splenectomy as well as in those who have not [10]. In contrast, IV anti-D is effective primarily in Rh+ patients who have not undergone splenectomy [14].

In 1997, a correlation was reported in 30 children and adults with ITP between the acute platelet response to IVIG and the longterm response to subsequent splenec-

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tomy [18]. The study described here was designed to investigate whether response to IV anti-D was related to the response to subsequent splenectomy. In addition, it was anticipated that many of the patients would also have received IVIG and that this subset could be used to further explore the correlation of IVIG response with response to splenectomy and to explore the relationship of response to IV anti-D and response to IVIG.

METHODS

Patients

Clinical information describing patients who had received IV anti-D and then proceeded to splenectomy was sought from two sources of patients treated prior to licensure of IV anti-D (Winrho-SDF): first, from 261 previously reported patients who had received their initial IV anti-D treatment at New York Presbyterian Hospital from 1987 to 1994 [13,14], and second, from patients who had been enrolled in the Cangene Corporation's (then Rh Pharmaceuticals, Winnipeg, Canada) compassionate treatment study with IV anti-D in the United States and Canada from 1988 to 1993 who were not among the 261 patients indicated above. HIV-infected patients were excluded from the study as were patients who did not have platelet counts available for at least 1 year after splenectomy.

IRB approval at New York Presbyterian Hospital was obtained to perform this followup study. In addition, Cangene Corporation designated two of the authors (J.B. and C.K.) as their agents to obtain followup information regarding the patients in the compassionate treatment study.

Patient Data

The 156 HIV-uninfected patients among the 261 patients treated at New York Presbyterian Hospital had their records reviewed and/or their current physicians called to obtain updated information as to whether they had undergone splenectomy and, if so, what their platelet response to splenectomy had been.

Patients in the Cangene compassionate use study (29 adults and 112 children) were identified from previously completed case report forms as to whether they had undergone splenectomy. The patients who had undergone splenectomy had their followup data pursued for this study.

For both sets of patients, information was sought regarding response to additional IV anti-D infusions and to IVIG (if used). Hemoglobin values were tabulated where available. Only 14 patients were on concomitant, tapering prednisone at the time of their infusions of IV anti-D or IVIG.

Data Analysis

In analyzing the response to IV anti-D and to IVIG, the criteria used to define response were taken from the previously published study exploring IVIG response [18]. Specifically, a peak platelet count $<50{,}000/\mu l$ following IV anti-D or IVIG treatment was defined as a poor response; one of $\geq 50{,}000/\mu l$ was defined as a "good–excellent response". These platelet counts were taken from the peak count available within the first week following treatment, usually on Day 7. For splenectomy response, any patient who had a platelet count $<50{,}000/\mu l$ or who required medical treatment for ITP after surgery was defined as a poor responder. To be considered a good–excellent responder, patients' platelet counts had to remain above $50{,}000/\mu l$ and require no treatment for a minimum of 12 months after surgery. Also according to the previous study, an "adult" was defined as ≥ 15 years of age [18].

Many of the patients received more than one course of treatment with IV anti-D and with IVIG. The primary analysis used the response to the initial courses of IV anti-D and of IVIG. Data from the last presplenectomy treatment with IV anti-D and IVIG were also used to explore a relationship to splenectomy when these were available. Three children and five adults had uninformative last IV anti-D infusions, because they received them immediately prior to splenectomy, and 10 patients received only a single dose of IV anti-D, leaving a total of 43 patients for analysis of effects of the last anti-D infusion. Similarly, only 23 of 38 patients treated with IVIG had information describing the most recent infusion prior to splenectomy.

"Congruent" responses were considered those in which the response to the two treatments was the same: "good" to anti-D (or IVIG) and "good" to splenectomy *or* "poor" to anti-D and "poor" to splenectomy. "Discrepant" responses were those with opposite responses, i.e., "good" to anti-D but "poor" to splenectomy.

Statistics

To compare the responses to the treatments, the Fisher's exact test was used since, especially in the subgroup analyses, there were occasionally insufficient values in one of the four cells to use the chi-square test.

RESULTS

Evaluable Patients

There were 156 eligible (HIV-uninfected, HIV-) patients from the New York Presbyterian Hospital study of patients treated from 1987 to 1994. Of these 156 patients, long-term followup information was available in 110 patients (71%). Sixty-seven did not undergo splenectomy as of their most recent followup visit, and 53 underwent

TABLE I. Rate of Good Response to Treatments

	All patients	Adults	Children
IV Anti-D[a]	37/61 (61%)	18/24 (75%)	19/37 (51%)
IVIG[a]	29/38 (76%)	9/12 (75%)	20/26 (77%)
Splenectomy[b]	41/61 (67%)	16/24 (67%)	25/37 (68%)

[a]Good response = a platelet count ≥50,000/μl following IV anti-D or IVIG.
[b]Good response = a platelet count remaining above 50,000/μl for a minimum of 12 months following splenectomy.

splenectomy. Of the 53 patients known to have undergone splenectomy, 11 patients did not have information available for 1 year after splenectomy, leaving 42 evaluable patients (80%).

Among the 141 patients included in the Cangene (Rh Pharmaceutical) compassionate study, 37 HIV− patients were known to have subsequently undergone splenectomy. Eighteen patients could not be included because their treating physicians did not have platelet counts at least 1 year after splenectomy, leaving 19 patients in whom platelet responses to IV anti-D and to splenectomy were available for analysis.

The 61 patients in this long-term followup study included 37 children (mean age 8 years, range 3–14 years) and 24 adults (13 patients between age 15–18 years and 11 patients > 18 years of age). Forty-three patients had information available describing platelet responses to a subsequent infusion of IV anti-D (see Methods). In 38 of the total of 61 patients, data were available regarding response to initial IVIG; 23 of these 38 patients had information available describing response to a subsequent IVIG infusion prior to splenectomy.

The mean time from diagnosis to splenectomy was 3 years with a range of 1–528 months.

Response to the Individual Treatments

The overall response rates to IV anti-D, IVIG, and splenectomy of all the patients in the study are indicated in Table I, including separation of children and adults.

Response to Initial IV Anti-D Treatment and to Splenectomy (Table II)

There was not a significant relationship between anti-D response and response to subsequent splenectomy in the 61 patients in this study. Furthermore, individual patients could not be selected for or reserved from splenectomy on the basis of their response to IV anti-D. Specifically, there were 10 patients with a good response to IV anti-D yet a poor response to subsequent splenectomy, and there were 14 patients with poor responses to IV anti-D but good responses to splenectomy (Table II). Neither children nor adults had a substantially better relationship (Tables IIA and IIB) than that seen in the overall group. There was no difference between good and poor responders in the initial dose of IV anti-D: 38 μg/kg, range 22–63, compared to 37 μg/kg, range 24–50.

TABLE II. Relationship of Responses: First Anti-D Infusion Versus Splenectomy (All), *N* = 61

Splenectomy response[a]	***Good***	14	27
	Poor	10	10
	NS[d] ($P = 0.11$)	***Poor***	***Good***
		Anti-D Response[b]	
(A) First Anti-D Infusion Versus Splenectomy (Adults), $N = 24$			
Splenectomy response[a]	***Good***	3	13
	Poor	3	5
	P = NS[c]	***Poor***	***Good***
		Anti-D Response[b]	
(B) First Anti-D Infusion Versus Splenectomy (Children), $N = 37$			
Splenectomy response[a]	***Good***	11	14
	Poor	7	5
	NS[d] ($P = 0.20$)	***Poor***	***Good***
		Anti-D Response[b]	

[a]As 1 year platelet count.
[b]As 1 week platelet count.
[c]Not significant (NS) if $P > 0.20$.
[d]Not significant (NS) if $P = 0.06$–0.20 (value provided).

Response to Last IV Anti-D Treatment and to Splenectomy (Table III)

There was a relationship of response to the last infusion of IV anti-D prior to splenectomy and response to splenectomy in the 43 evaluable patients (Table III, $P = 0.01$). There was no difference between good and poor responders in the last dose of IV anti-D: 43 μg/kg, range 18–75, compared to 42 μg/kg, range 24–62. This relationship was based primarily on the 14 adults among whom there was only 1 patient with a discrepant response: response good to last anti-D but poor to subsequent splenectomy (Table IIIA, $P = 0.003$). Note that five of these 14 adults changed their responses from "discrepant" to "congruent" from their initial to their last anti-D, explaining the better relationship with the last infusion. Three patients who later failed splenectomy no longer responded to anti-D whereas 2 initial nonresponders to anti-D became responders and subsequently did well with splenectomy. There was no relationship of the response to the last anti-D and response to splenectomy among children: 12 of the 29 children had discrepant responses (Table IIIB).

Hemolysis Following Initial IV Anti-D and Response to Splenectomy (Table IV)

There was a significant relationship between a larger hemoglobin decrease, Day 7 hemoglobin minus Day 0 hemoglobin, and better response to splenectomy ($P = 0.03$). Specifically, in the 7 patients whose hemoglobin decrease after the initial IV anti-D treatment was ≥2.0 g/dl, all responded to subsequent splenectomy; 2 did not have a platelet response to anti-D. These 7 patients with hemoglobin decreases ≥2.0 g/dl received a mean IV

TABLE III. Last Anti-D Infusion Versus Splenectomy (All), *N* = 43

Splenectomy response[a]	***Good***	9	20
	Poor	10	4
	$P = 0.01$	***Poor***	***Good***
			Anti-D Response[b]
(A) Last Anti-D Infusion Versus Splenectomy (Adults), $N = 14$			
Splenectomy response[a]	***Good***	0	8
	Poor	5	1
	$P = 0.003$	***Poor***	***Good***
			Anti-D Response[b]
(B) Last Anti-D Infusion Versus Splenectomy (Children), $N = 29$			
Splenectomy response[a]	***Good***	9	12
	Poor	5	3
	$P =$ NS[c]	***Poor***	***Good***
			Anti-D Response[b]

[a]As 1 year platelet count.
[b]1 week post anti-D.
[c]Not significant (NS) if $P > 0.20$.

TABLE IV. Hemolysis After First Anti-D Treatment Versus Splenectomy (All), *N* = 40

Splenectomy response[a]	***Good***	18	7
	Poor	15	0
	$P = 0.03$	***0.0–1.9 g/dl***	***≥2.0 g/dl***
			HGB Decrease[b]
(A) Hemolysis After First Anti-D Treatment Versus Splenectomy (Adults), $N = 19$			
Splenectomy response[a]	***Good***	10	2
	Poor	7	0
	$P =$ NS[c]	***0.0–1.9 g/dl***	***≥2.0 g/dl***
			HGB Decrease[b]
(B) Hemolysis After First Anti-D Treatment Versus Splenectomy (Children), $N = 21$			
Splenectomy response[a]	***Good***	8	5
	Poor	8	0
	NS[d] ($P = 0.06$)	***0.0–1.9 g/dl***	***≥2.0 g/dl***
			HGB Decrease[b]

[a]As 1 year platelet count.
[b]1 week post anti-D.
[c]Not significant (NS) if $P > 0.20$.
[d]Not significant (NS) if $P = 0.06$–0.20 (value provided).

anti-D dose of 32 μg/kg (range 22–45 μg/kg) compared to a mean dose of 38 μg/kg (range 24–63 μg/kg) in those patients with a hemoglobin decrease <2.0 g/dl. The relationship was nearly significant in children (Table IVB, $P = 0.06$) but not in adults (Table IVA).

There were only 21 patients evaluable for hemoglobin decrease following the last dose of anti-D and 4 had hemoglobin decreases >2.0 g/dl. These 4 patients also had a good response to splenectomy. CDE phenotyping to evaluate the possibility that anti-"e" and anti-"c" antibodies contributed to the degree of hemolysis was not performed in this study.

Response to IVIG and Response to Splenectomy (Tables V and VI)

Among the 38 of 61 IV anti-D-treated patients for whom IVIG response data were available, there was no relationship of response to IVIG and response to subsequent splenectomy. Specifically, 19 of 38 (50%) patients had discrepant responses: 12 patients had a good response to IVIG but a poor response to subsequent splenectomy; and 7 patients who did not respond well to IVIG had a good response to splenectomy. Neither children nor adults had a significantly better correlation of splenectomy response to response to IVIG (Tables VA and VB).

TABLE V. First IVIG Infusion Versus Splenectomy (All), *N* = 38

Splenectomy response[a]	***Good***	7	17
	Poor	2	12
	NS[d] ($P = 0.19$)	***Poor***	***Good***
			IVIG Response[b]
(A) First IVIG Infusion Versus Splenectomy (Adults), $N = 12$			
Splenectomy response[a]	***Good***	2	6
	Poor	1	3
	$P =$ NS[c]	***Poor***	***Good***
			IVIG Response[b]
(B) First IVIG Infusion Versus Splenectomy (Children), $N = 26$			
Splenectomy response[a]	***Good***	5	11
	Poor	1	9
	NS[d] ($P = 0.19$)	***Poor***	***Good***
			IVIG Response[b]

[a]As 1 year platelet count.
[b]1 week post IVIG.
[c]Not significant (NS) if $P > 0.20$.
[d]Not significant (NS) if $P = 0.06$–0.20 (value provided).

TABLE VI. Last IVIG Infusion Versus Splenectomy (All), *N* = 23

Splenectomy response[a]	***Good***	6	9
	Poor	5	3
	$P =$ NS[c]	***Poor***	***Good***
			IVIG Response[b]
(A) Last IVIG Infusion Versus Splenectomy (Adults), $N = 6$			
Splenectomy response[a]	***Good***	1	4
	Poor	0	1
	$P =$ NS[c]	***Poor***	***Good***
			IVIG Response[b]
(B) Last IVIG Infusion Versus Splenectomy (Children), $N = 17$			
Splenectomy response[a]	***Good***	5	5
	Poor	5	2
	$P =$ NS[c]	***Poor***	***Good***
			IVIG Response[b]

[a]As 1 year platelet count.
[b]1 week post IVIG.
[c]Not significant (NS) if $P > 0.20$.

Table VI demonstrates that the response to the last dose of IVIG prior to splenectomy, unlike for IV anti-D, was not correlated to nor predictive of response to subsequent splenectomy with 9 of 23 "discrepant" responses.

Response to IV Anti-D and Response to IVIG (Table VII)

There was no relationship of response to IV anti-D and response to IVIG. Specifically there were 15 patients

TABLE VII. Response to First IV Anti-D versus Response to First IVIG (All), *N* = 36

IVIG	***≥50 K/μl***	15	12
	<50 K/μl	4	5
	Platelet count[a]	***<50 K/μl***	***≥50 K/μl***
	P = NS[b]	IV Anti-D	
Response to first IV Anti-D versus Response to First IVIG (Adults), *N* = 11			
IVIG	***≥50 K/μl***	3	5
	<50 K/μl	1	2
	Platelet count[a]	***<50 K/μl***	***≥50 K/μl***
	P = NS[b]	IV Anti-D	
Response to First IV Anti-D versus Response to First IVIG (Children), *N* = 25			
IVIG	***≥50 K/μl***	12	7
	<50 K/μl	3	3
	Platelet count[a]	***<50 K/μl***	***≥50 K/μl***
	P = NS[b]	IV Anti-D	

[a]Platelet count following IV anti-D and IVIG.
[b]Not significant (NS) if $P > 0.20$.

who had a peak platelet count >50,000/μl following IVIG but a peak count <50,000/μl with IV anti-D; conversely there were 5 patients who had peak platelet counts >50,000/μl following IV anti-D and peak platelet counts <50,000/μl following IVIG.

DISCUSSION

Prediction of platelet response to splenectomy in patients with ITP has long been sought. However, no study has reported a readily available technique that reliably predicts response to splenectomy. The spleen has at least two seemingly distinct roles in ITP: filtration of antibody-coated particles and production of auto (anti-platelet) antibodies [19,20], which may explain the difficulty in prediction of response. Studies have attempted to predict splenectomy response according to the site of clearance (liver, spleen, or marrow) or lifespan of radiolabeled platelets [21,22], but these studies have not been confirmed [4,23]. Clinical prediction of a successful splenectomy has also been difficult [24]. Those patients with Evans syndrome [25], the combination of ITP and autoimmune hemolysis, and those with active systemic lupus erythematosus [26] (reviewed in reference 4) are thought to have lower response rates to splenectomy. Response to prednisone has been equivocal at best in predicting response to splenectomy [5,8,27]. Cases initially considered to be ITP may actually represent an early stage of marrow failure [28], as illustrated by one of the cases described by Law et al. [18]. One report has suggested that long platelet survival, i.e., low platelet turnover, which may include these marrow failure cases, may predict a poor response to splenectomy [29]. However, these studies are available only at a very small number of centers and may only predict response in a minority of patients.

The report by Law et al. described a statistically significant relationship of response to IVIG and response to splenectomy in 30 patients [18]; all but two of their patients had congruent responses to the two treatments. In contrast, in the 38 IVIG-treated patients reported here, 19 of the 38 patients had discrepant responses to IVIG and to splenectomy (Table V). Using the last infusion of IVIG did not improve the relationship. A clear explanation of the discrepancy in results is not apparent. Identical definitions of response were used. There were 21 adults in the Law study [18], and only 12 adults among our 38 patients, but 5 of the 12 adults in our study had discrepant responses between IVIG and splenectomy (Table VA). The patients in the Law study tended to receive IVIG and then proceed to splenectomy within the initial months of their diagnosis of ITP while the patients reported here received the IVIG and especially the splenectomy later in their course (an average of 3 years from diagnosis) and also received IV anti-D. The response rates to the 3 treatments reported here (Table I) are generally consistent with reported response rates [12–14,28–30], although there is a slightly lower than expected rate of response of children to both IV anti-D (51%) and to splenectomy (68%).

The published relationship of response to IVIG and response to splenectomy led us to hypothesize that IV anti-D might share a similar relationship, in part because IV anti-D also relies on Fc receptor blockade and also because the response to IV anti-D is clearly affected by whether the patient has been previously splenectomized [13,14,30]. The failure of response to the initial infusion of IV anti-D to predict response to splenectomy was therefore disappointing. The possible relationship of response to the last IV anti-D infusion prior to splenectomy with the response to subsequent splenectomy would incorporate a temporal factor regarding the state of the ITP potentially explaining the better relationship. Why this relationship was identified in adults but not children is unclear. Similarly, the good response to splenectomy in all 7 patients with the greatest degree of hemolysis in response to their initial IV anti-D also requires confirmation. Since the doses of IV anti-D in μg/kg were not greater in the group with increased hemolysis, the relationship presumably reflects the removal of a "hyperactive filter" of antibody-coated red blood cells and, by inference, of antibody-coated platelets.

We took advantage of the collected information describing response to treatment to compare response to IVIG with response to IV anti-D. Surprisingly, there was a lack of correlation of the responses. This suggests that despite the "common" mechanism of Fc blockade, the two treatments may do this differently, and this difference may be important in patients with ITP. It is not clear whether the relationships would have been changed if "current" doses of IV anti-D, i.e., 75 μg/kg, had been

used. In particular, the results in Table VII comparing IVIG and IV anti-D and the results in Table II comparing response to IV anti-D and response to splenectomy might have been different if a larger dose of IV anti-D had been used.

CONCLUSION

This study did not identify a simple relationship of initial response to IV anti-D and response to subsequent splenectomy ($n = 61$) nor of splenectomy response and response to IVIG ($n = 38$). In two subgroups, there were apparent relationships of IV anti-D response to splenectomy response, one in adults utilizing the last infusion of IV anti-D and the other based upon a greater degree of hemolysis. These findings in small subgroups of patients require confirmation. The failure to identify overall relationships of responses to IVIG, IV anti-D, and splenectomy highlights the complex nature of splenic function in particular and platelet production and destruction in general in patients with ITP.

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