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Response to Steroids Predicts Response to Rituximab in Pediatric Chronic Immune Thrombocytopenia

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Abstract

Background—Treatment choice in pediatric immune thrombocytopenia (ITP) is arbitrary, because few studies are powered to identify predictors of therapy response. Increasingly, rituximab is becoming a treatment of choice in those refractory to other therapies.

Methods—The objective of this study was to evaluate univariate and multivariable predictors of platelet count response to rituximab. After local IRB approval, 565 patients with chronic ITP enrolled and met criteria for this study in the longitudinal, North American Chronic ITP Registry (NACIR) between January 2004 and October 2010. Treatment response was defined as a post-treatment platelet count ≥50,000/μl within 16 weeks of rituximab and 14 days of steroids. Treatment response data were captured both retrospectively at enrollment and then prospectively.

Results—Eighty (14.2%) patients were treated with rituximab with an overall response rate of 63.8% (51/80). Univariate correlates of response to rituximab included the presence of secondary ITP and a positive response to steroids. In multivariable analysis, response to steroids remained a strong correlate of response to rituximab, OR 6.8 (95% CI 2.0–23.0, $P = 0.002$). Secondary ITP also remained a strong predictor of response to rituximab, OR 5.6 (95% CI 1.1–28.6, $P = 0.04$). Although 87.5% of patients who responded to steroids responded to rituximab, 48% with a negative response to steroids did respond to rituximab.

Conclusion—In the NACIR, response to steroids and presence of secondary ITP were strong correlates of response to rituximab, a finding not previously reported in children or adults.

Keywords

ITP; pediatric; rituximab; treatment

Introduction

Pediatric chronic immune thrombocytopenia (ITP) has an incidence of 1–2 per 100,000. Baseline bleeding complications and platelet counts can be variable in different patients with chronic ITP and the decisions about whom and when to treat are challenging. Few studies are powered to identify predictors of therapy response in ITP. A number of previous studies have examined whether response to steroids and IVIG predict response to sple-nectomy [1–11]. However, these studies have had mixed results. Therefore, treatment choices in pediatric chronic ITP remain arbitrary.

Splenectomy is often an early treatment choice in adults with symptomatic ITP [12,13]. Since pediatric ITP patients have a longer-term risk for post-splenectomy sepsis and a higher rate of spontaneous remission when in the chronic phase, many physicians are often hesitant to recommend splenectomy in this population [14]. Increasingly, rituximab is becoming a treatment of choice in pediatric patients refractory to other therapies [14]. Previous studies in children have shown a variable response to rituximab, ranging from 20% to 69% [15–18]. However, these studies tend to be small enough such that the 95% confidence intervals on success rates overlap substantially. With this wide therapeutic effect, predictors of response to rituximab in this population would clearly be of utility.

The goal of this study was to evaluate univariate and multi-variable predictors or correlates of platelet count response to rituximab in patients enrolled in the North American Chronic ITP Registry (NACIR).

Methods

The NACIR is an ongoing longitudinal, observational, cohort, including 572 patients withchronic ITP enrolled between January 2004 and October 2010. The NACIR is one of the largestlongitudinal datasets of children and adolescents with chronic ITP and includes 16 sites in theUnited States and Canada (Supplemental Tables I and II). The protocol was approved by the Investigational Review Board at each site, and informed consent was obtained prior to the enrollment of each patient.

Eligibility for registry enrollment included: ages 6 months–18 years at ITP diagnosis, a clinical diagnosis of ITP, and ITP duration >6 months. Misdiagnoses of ITP in subjects after enrollment were recorded by site in the data entry system. Demographic information, laboratory data, bleeding observations, and previous treatments and responses were collected at enrollment. Detailed information regarding ongoing treatments, response, and side effects to therapies was recorded prospectively.

Definitions

“Primary ITP” was defined as isolated thrombocytopenia without associated conditions. “Secondary ITP” included those patients with ITP associated with other immune-mediated medical conditions, including Evans syndrome and Lupus. Acute (<6 months from diagnosis of ITP) and chronic ITP (≥6 months from diagnosis of ITP) were defined when the NACIR began enrollment using historical criteria prior to the 2009 terminology changes. “Treatment response” was defined as a post-treatment platelet count ≥50,000/μl within 16 weeks of rituximab or within 14 days of steroids. Steroids were prescribed as 1–4 mg/kg/day of prednisone (or its equivalent if another steroid was employed) for ≤14 days with or without taper. A treatment non-responder was defined as an individual who did not meet criteria for “treatment response.” The NACIR captured treatment responses both retrospectively (from chart review of the period prior to enrollment) and then prospectively, and both periods were included in this analysis. Data about the order and timing of treatments and the duration of treatment response were only available for the prospectively captured data and not accounted for in this analysis.

Statistical Methods

The objective of the analysis was to identify predictors of response to rituximab with clinical information that would be available prior to treatment. Initial analysis compared the subset of patients who received rituximab with those who did not, using Fisher's exact test, the Cochran–Armitage trend test (for ordered categorical variables), or the Wilcoxon rank sum test. For the univariate analysis examining the predictors of response to rituximab, variables were selected among demographic, clinical, and laboratory values by clinical significance and response rates were compared with Fisher's exact test. For the multivariable logistic regression modeling, a total of five variables were deemed clinically significant or statistically promising based on the univariate analysis.

The rest of the modeling process utilized the LOGISTIC procedure in SAS 9.1 to perform multivariable logistic regression. Associations were expressed as odds ratios (OR). Several continuous factors were categorized using clinically meaningful cut-points. Ultimately, all variables in our regression model were binary. A backwards elimination selection procedure was used to select the final multivariable model. No adjustments have been made for multiple comparisons. All *P*-values were two sided.

Factors with missing data were transformed into pairs of binary variables: one indicating absence of data and the other indicating the outcome of interest. The pair of variables was

always considered together in a model, but the pair was retained or dropped based only on the parameter of interest, and only this parameter was reported. This procedure allowed patients with missing data on some predictors to remain in the multivariable models, thus contributing information when present.

Results

Of 572 patients enrolled in the NACIR from January 2004 through October 2010, a total of 7 subjects did not have chronic ITP and were excluded from this analysis. Eighty (14.2%) of the remaining 565 patients were treated with rituximab. Table I compares the characteristics of these patients with those who were not treated with rituximab. Those patients treated with rituximab were more likely to have secondary ITP, including Evans Syndrome (23.7% vs. 10.5%, $P < 0.01$). Of the 19 patients with secondary ITP who were treated with rituximab, 14 had Evans syndrome, 1 had Lupus-related ITP, and 4 had other ITP-associated autoimmune diseases. Those treated with rituximab were also more likely to have a positive direct anti-globulin test (33.3% vs. 20.3%, $P = 0.05$). In addition, patients treated with rituximab were more likely to have a lower platelet count, most significantly at the time of diagnosis of chronic ITP (median platelet count 14,000 cells/μl vs. 40,000 cells/μl, $P < 0.01$). Those patients treated with rituximab were more likely to have experienced a higher severity grade of their worst documented hemorrhage at any point during their diagnosis with ITP ($P = 0.02$) [19]. A greater percentage of non-Caucasian patients was treated with rituximab compared with those who were not ($P = 0.05$). In general, patients treated with rituximab tended to be of the same age and gender as those who did not receive rituximab.

Univariate Analysis

Patients treated with rituximab had an overall initial response rate of 63.8% (51/80). The strongest univariate correlate of response to rituximab (Table II) was a “treatment response” to steroids (5- to 14-day course) with an OR 7.6 ($P < 0.01$). Of the 32 patients who responded to steroids, 28 (87.5%) responded to rituximab compared with only 23 (47.9%) of 48 patients who did not respond to steroids.

The only other significant univariate predictor of response to rituximab was the diagnosis of secondary ITP (OR 6.76, $P < 0.01$). Gender, ethnicity, and race were not predictive of response to rituximab. Furthermore, other variables which did not predict rituximab response include: history of a bleeding score ≥3, symptoms ≥1 month prior to ITP diagnosis, age >10 years, platelets ≥20,000/μl at acute or chronic ITP diagnosis, response to IVIG, and a positive ANA.

Multivariable Analysis

In multivariable analysis, five variables were entered into the initial model based on clinical significance and univariate analysis results. These variables included: response to steroids, response to IVIG, presence of secondary ITP, platelet count at the diagnosis of chronic ITP, and age. Two variables were found to be independent correlates of response to rituximab. Response to steroids remained a strong correlate of response to rituximab with an OR 6.8 (95% CI 2.0–23.0, $P = 0.002$). Secondary ITP also remained a strong predictor of response to rituximab with an OR 5.6 (95% CI 1.1–28.6, $P = 0.04$).

Discussion

In the NACIR, a positive platelet response to steroids was a strong correlate of a platelet response to rituximab (odds ratio 6.8), a finding not previously reported in children or adults with ITP. Secondary ITP was also an independent predictor of rituximab response. The

relatively high proportion of patients in the registry receiving rituximab (80/565) is consistent with a survey of members of the American Society of Pediatric Hematology/ Oncology, so is not unique to the 16 sites in the NACIR [14]. Patients with higher severity bleeding scores and secondary ITP were more likely to receive rituximab. The fact that patients receiving rituximab experienced more severe hemorrhage is not surprising, since ITP patients with bleeding are less likely to be observed and, therefore, more likely to receive second- or third-line therapies. In addition, it is also not surprising that a high proportion of secondary ITP patients received rituximab, given that secondary ITP is often more refractory to alternative treatments than primary ITP.

Published response rates to rituximab in children with ITP vary widely, with overall response rates ranging from 20% to 65% [15–18]. What accounts for the variability in rituximab response? One possibility could be the fraction of steroid refractoriness of the study population. Based on our current results, the studies with more steroid-refractory ITP patients might report a lower overall rituximab response rate, as has been documented in a few such studies [18]. A second possible explanation for inter-study variability in rituximab response would be differing percentages of patients with secondary ITP. Thus, studies with the highest percentages of secondary ITP patients would have the higher rituximab response rates, an observation previously made by others [20]. Finally, many of the studies reporting rituximab response rates are much smaller in size than the current study.

Although factors predictive of response to rituximab in ITP patients have not been validated, a number of positive clinical predictors have been reported for adult ITP patients, including younger age, newly diagnosed disease, absence of splenectomy, and fewer treatments prior to rituximab [15,21–24]. One previous pediatric ITP study identified the following factors as positive predictors of response to rituximab: newly diagnosed disease, older age at diagnosis, and a higher platelet count at diagnosis [17]. From our NACIR data set, we could not confirm any of these previously reported predictive clinical factors in our pediatric ITP population. Furthermore, this previously reported study involving children did not report whether response to steroids or the presence of secondary ITP were predictive of response to rituximab [17].

Current understanding of the mechanism of glucocorticoids for treatment of ITP is through an effect on both the T and B cell arms of the immune system. Rituximab, an anti-CD20 antibody, binds to and leads to death of pre-B through mature B cells; secondary T-cell effects are also reported [25,26]. It may be that the overlapping biology of glucocorticoids and rituximab action explain the ability of steroid response to predict rituximab response. In this study, patients with secondary ITP, in whom the majority had Evans syndrome, were more likely to respond to rituximab. Patients with secondary ITP, as a group, may be less heterogeneous in terms of the underlying immune dysfunction, and, therefore, may be more likely to respond similarly to certain treatments. This is consistent with previously reported high rates of response to rituximab in those patients with secondary ITP [20,27].

In this study, patients who responded to steroids were very likely to respond to rituximab (87.5%). However, of the 48 patients who did not respond to steroids, 23 (48%) still responded to rituximab. Therefore, utilizing this study's finding in clinical care must be done with caution, as many steroid-refractory ITP patients may still respond to rituximab. The finding that could be utilized clinically is the high rate of rituximab response in those patients who were steroid responsive.

This study has a number of limitations: the majority of treatment data were collected retrospectively at enrollment, and data about the duration of platelet response were not available. Therefore, we cannot comment about the duration of platelet response or the

impact of the time frame between steroid course(s) to rituximab treatment or from diagnosis to rituximab treatment, both of which may be important in determining rituximab response. Steroids were presumably used prior to rituximab in most cases, but these data on treatment timing are also lacking from the retrospective NACIR information. Thus, the concept that the steroid response predicts rituximab response is based on inference.

In summary, the present data provide circumstantial evidence that rituximab should be most considered in secondary ITP patients and ITP patients previously responsive to steroids. To the extent that prednisone is validated as a robust prospective predictor, this finding could change clinical ITP practice with regard to rituximab utilization. These relationships require further validation in both adult and pediatric ITP studies. We encourage other investigators to prospectively evaluate the relationships between steroid responsiveness, the presence of secondary ITP, and response to rituximab.

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Table I

Comparison of the Clinical and Laboratory Characteristics of the North American Chronic ITP Registry by Whether Patients Were Treated With Rituximab

	NACIR patients: no rituximab	NACIR patients: treated with rituximab	*P*-value
Total number of subjects (n)	485	80	
Median age at diagnosis (years)	8.6 (IQR 4.2, 12.8)	7.5 (IQR 4.9, 12.0)	0.59
Ages 0–2	10.9%	18.8%	
Ages >2–10	46.0%	45.0%	
Ages >10	43.1%	36.3%	
Gender (male)	46.4%	43.8%	0.72
Race			0.05
Caucasian	70.5%	61.3%	
Black	4.7%	12.5%	
Asian	6.0%	7.5%	
Other/unknown	18.8%	18.7%	
Hispanic	20.3%	17.5%	0.73
Median platelet count at acute ITP diagnosis (kcells/μl)	13 (IQR 6, 33)	10 (IQR 5, 20)	0.03
Median platelet count at chronic ITP diagnosis (kcells/μl)	40 (IQR 20, 71)	14 (IQR 8, 35)	<0.01
Primary ITP	89.5%	76.3%	<0.01
Secondary ITP	10.5%	23.7%	
Evans syndrome	6.8%	17.5%	
Antecedent viral illness	28.1%	22.1%	0.33
Positive ANA (>1:40)	28.4%	29.6%	0.87
Direct anti-globulin positive[a]	20.3%	33.3%	0.05
Median duration of symptoms before Diagnosis of ITP (months)	0.47 (IQR 0.07, 2)	0.23 (IQR 0.06, 1)	0.38
Worst documented bleeding[b]			<0.01
Grade 0	28.4%	18.8%	
Grade 1	40.1%	35.0%	
Grade 2	22.8%	23.8%	
Grade 3	8.6%	21.3%	
Grade 4	0.2%	1.3%	

IQR, interquartile range; SD, standard deviation.

[a] Including transiently positive results with a normal hemoglobin as well as post-anti-D globulintreatment positive results;

[b] By modified Buchanan and Adix Bleeding Score [19]. No patients had fatal bleeds.

Table II

Univariate Analysis of Platelet Response* to Rituximab

	Rituximab response			
Characteristic	**#/N (%)**	**OR**	**95% CI**	***P*-value**
All patients	**51/80 (63.8%)**			
Platelet response* to steroids				
Yes	**28/32 (87.5%)**	**7.61**	**2.31–25.03**	**0.0003**
No	**23/48 (47.9%)**			
ITP diagnosis				
Secondary	**17/19 (89.5%)**			
Primary	**34/61 (55.7%)**	**6.76**	**1.43–32.26**	**0.007**
Platelet count at chronic ITP diagnosis				
≥20,000/μl	23/30 (76.7%)			
<20,000/μl	28/50 (56.0%)	2.58	0.94–7.11	0.09
Platelet response* to IVIG				
Yes	28/38 (73.7%)			
No	23/42 (54.8%)	2.31	0.9–5.94	0.1
Race				
Caucasian	34/49 (69.4%)			
Non-Caucasian	17/31 (54.8%)	1.87	0.74–4.74	0.24
ANA				
Positive	13/16 (81.3%)			
Negative	24/38 (63.2%)	2.53	0.61–10.43	0.34
Antecedent viral illness				
Yes	9/17 (52.9%)			
No	40/60 (66.7%)	0.56	0.19–1.68	0.39
Bleeding score[a]				
Bleeding score ≥3	22/37 (59.5%)			
Bleeding score <3	29/43 (67.4%)	0.71	0.28–1.77	0.49
Platelets at acute ITP diagnosis				
≥20,000/μl	12/17 (70.6%)	1.48	0.46–4.71	0.58
<20,000/μl	39/63 (61.9%)			
Gender				
Male	21/35 (60.0%)			
Female	30/45 (66.7%)	0.75	0.30–1.88	0.64
Ethnicity				
Hispanic	6/11 (54.5%)			
Non-Hispanic	33/52 (63.5%)	1.45	0.39–5.39	0.73
Length of symptoms prior to diagnosis				
≥1 month	10/14 (71.4%)	1.33	0.36–4.93	0.76
<1 month	30/46 (65.2%)			

	Rituximab response			
Characteristic	**#/N (%)**	**OR**	**95% CI**	***P*-value**
Age at diagnosis of acute ITP				
>10 years	19/29 (65.5.%)			1
≤10 years	32/51 (62.7%)	1.13	0.44–2.93	
Direct anti-globulin test				
Positive	13/18 (72.2%)			
Negative	26/36 (72.2%)	1.00	0.28–3.53	1

OR = odds ratio. Significant predictors in bold. Subjects with an unknown characteristic are excluded for analysis of that characteristic.

*Platelet response defined as a post-treatment platelet count ≥50,000/μl;

[a]By modified Buchanan and Adix Bleeding Score [19].