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BRIEF REPORT

Response to rituximab in children and adults with immune thrombocytopenia (ITP)

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Abstract

Background: Rituximab is a monoclonal anti-CD20 antibody used as a second-line treatment for immune thrombocytopenia (ITP). As additional treatments for ITP emerge, identifying the most appropriate patients and optimal timing for rituximab are important but challenging without established predictors of response to therapy.

Objectives: The purpose of this study was to describe demographic, clinical, and laboratory characteristics of pediatric and adult patients with ITP to identify differences in evaluation before rituximab administration and correlates of platelet response.

Methods: This is a retrospective cohort study describing the characteristics of patients with ITP treated with rituximab from 2010 to 2020 at two academic tertiary care centers.

Results: A total of 64 patients met criteria for inclusion. Complete rituximab response (56%) was not significantly different between children (58%, n = 24) and adults (55%, n = 40). Response rate was similar in those with primary versus secondary ITP (53% vs 62%). Among patients treated with rituximab, Evans Syndrome was more common in children than adults (42% vs 18%). Immunologic labs assessed before rituximab varied by age and were more commonly evaluated in children (lymphocyte subsets 88% vs 22%). Immunologic markers, including antinuclear antibody, direct antiglobulin testing, immunoglobulin levels, and lymphocyte subsets, did not predict response to rituximab in pediatric or adult patients with ITP.

Conclusions: Pre-rituximab immunologic evaluation varied significantly between adults and children, which could represent institution-specific practice patterns or a more general practice difference. If the latter, underlying immunodeficiency in adults with ITP may be underrecognized. Standardized guidance for pre-rituximab immunologic evaluation is needed.

KEYWORDS
children, immune thrombocytopenia, ITP, rituximab, treatment

This work was conducted at Boston Children's Hospital, Boston, MA 02115.

Essentials

- Selecting rituximab to treat immune thrombocytopenia (ITP) is challenging without predictors of response.
- Features of patients with ITP treated with rituximab were collected from two academic centers.
- Although clinical features and labs evaluated varied by age, none predicted rituximab response.
- Pre-rituximab immunologic evaluation varies and recommendations for standardization are needed.

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired condition resulting in a platelet count $<100 \times 10^9$/L due to autoimmune destruction of circulating platelets and impaired thrombopoiesis. Approximately 5 to 10 in 100 000 children and 3.3 in 100 000 adults per year are affected by ITP.[1] The clinical presentation of ITP most commonly involves bruising, petechiae, and mucosal bleeding in patients with isolated thrombocytopenia. ITP in young children is often self-limited, whereas ITP in adults is more frequently chronic.[2,3]

Common goals of therapy in ITP include increasing the platelet count sufficiently to treat current bleeding and/or prevent subsequent hemorrhage and to improve health-related quality of life. Although many patients can be closely observed or managed with standard first-line agents, such as corticosteroids, intravenous immunoglobulin (IVIG), and intravenous anti-RhD immune globulin, others experience persistently low platelet counts and/or associated symptoms and are treated with second-line therapy. In the Pediatric and Adult Registry on Chronic ITP, 38% to 47% of children and 67% to 74% of adults with ITP required second-line therapies by 6 to 24 months.[4]

Second-line treatments for ITP include thrombopoietin receptor agonists, rituximab, and splenectomy, among others. Selecting among these options requires complex decision making.[5,6] Rituximab is a monoclonal anti-CD20 antibody with an initial response rate (platelet count $\geq 50\times10^9$/L) of 50% to 60% and 5-year sustained response of 25% to 30%.[7] There are conflicting studies reporting positive predictors of rituximab response, including prior response to corticosteroids, female sex, younger age, interval between diagnosis and rituximab treatment <24 months, and a diagnosis of secondary ITP.[8-10] Although rituximab has an overall reassuring safety profile, there are several potential risks to consider, including treating patients with underlying immunodeficiencies, as toxicities such as hypogammaglobulinemia and neutropenia have been reported.[11] A low baseline IgG level in patients receiving rituximab is a risk factor for severe infections.[12] Furthermore, a subset of patients develop prolonged hypogammaglobulinemia and/or impaired B-cell reconstitution after rituximab.[11,13] Despite these risks, there are no clear guidelines regarding immunologic testing before rituximab therapy in ITP. The aim of this study is to describe the demographic, clinical, and laboratory characteristics of pediatric and adult patients treated with ITP over the past 10 years at two academic tertiary care centers to identify correlates of platelet response to rituximab and differences in testing before rituximab administration between children and adults.

2 | METHODS

This retrospective cohort study was approved by the Boston Children's Hospital (BCH) and Massachusetts General Hospital (MGH) Institutional Review Boards. Patients met the following inclusion criteria: (i) assigned an International Classification of Diseases, Ninth Revision (ICD-9) code of 287.31 or an ICD, Tenth Revision (ICD-10) code of D69.3 (immune thrombocytopenic purpura); and (ii) received treatment with rituximab for ITP at BCH or MGH in either an inpatient or outpatient setting between January 2010 and December 2019, with clinical information in the electronic medical record (EMR). A total of 103 patients were initially identified, 42 patients treated at BCH and 61 patients treated at MGH. On review of medical records, 17 were excluded because they did not have ITP, 16 did not receive rituximab to treat ITP, 2 had received rituximab before implementation of the EMR, and 4 received their first dose of rituximab at an outside institution. Thus, a total of 64 patients were included in the final cohort.

Demographic and clinical characteristics, laboratory studies, and treatments were collected from EMR review. If IVIG or corticosteroids were administered before rituximab, platelet counts within 1 month after IVIG or corticosteroid administration were considered pre-treated and excluded from analysis. For immunologic laboratory tests, the earliest available value was included. The following definitions were used: positive antinuclear antibody (ANA) as ≥1:80, hypogammaglobinemia as IgG level <600 mg/dL, hypergammaglobulinemia as IgG level >2000 mg/dL, and low IgA as <7 mg/dL. Evans syndrome was defined as two or more immune cytopenias occurring concurrently or sequentially.

Complete response to rituximab was defined as at least one platelet count $\geq 100 \times 10^9$/L within 6 months after rituximab administration. Partial response to rituximab was defined as a platelet count $\geq 30 \times 10^9$/L and at least doubling of platelet count at diagnosis within 6 months after rituximab administration. Rituximab nonresponse was defined as not meeting complete or partial response criteria. Patients who required rescue treatment or other second-line ITP-directed therapies within 6 months after the first dose of rituximab were considered to have a rituximab nonresponse (Table S1). For analyses comparing response to nonresponse, response was defined using complete response. Phase of ITP at time of treatment was defined using standard definitions.[14] Response

to previous treatment with IVIG or corticosteroid was defined as a platelet count ≥100 × 10^9/L within 2 weeks of administration or documentation of complete response in a clinician note.

Descriptive statistics reported are frequencies and proportions for categorical variables and median and range for continuous variables. Fisher's exact test and the Wilcoxon rank-sum test are used to identify variables, categorical and continuous, respectively, that are associated with rituximab response. Sample sizes are presented for those with available data for each variable. Observational data were incomplete for some of the factors analyzed herein. *P* values were two-sided, and *P* values <.05 were considered statistically significant.

3 | RESULTS/DISCUSSION

The demographic and clinical characteristics of the cohort are described in Table 1. Twenty-four patients (38%) were <18 years old, and 40 (62%) were ≥18 years old at the time of the first rituximab dose. Twenty-one patients (32.8%) had secondary ITP. Seventeen patients (26.6%) had Evans syndrome, more commonly in those treated with rituximab at age <18 years compared to those ≥18 years (42% vs 17.5%; *P* = .04). The phase of ITP at the time of rituximab treatment did not differ by age group. The number of treatments received before rituximab also did not differ by age (median, 3; range, 1-7).

The immunologic labs assessed before rituximab varied by age and were performed more often in those aged <18 years. Although IgG levels were obtained in 83% of patients aged <18 years versus 85% of patients aged ≥18 years (*P* = 0.99), IgG subsets were evaluated in 54% of patients aged <18 years versus 8% of patients aged ≥18 years (*P* < .0001). Lymphocyte subsets were evaluated in 88% of patients aged <18 years versus 22% of patients aged ≥18 years (*P*<0.001). ANA was performed in 33% of patients aged <18 years and 60% of patients aged ≥18 years (*P* = .70). A direct antiglobulin test (DAT) was performed in 88% of patients aged <18 years and 75% aged ≥18 years. Those aged ≥18 years were more likely to have a positive DAT (0% <18 years versus 27% ≥18 years; *P*=.02). Positive ANA, hypergammaglobulinemia, hypogammaglobulinemia, low IgA, and low B-cell number were not significantly different by age (Table 1), and likelihood of rituximab response was also similar despite differences in the frequency that laboratory studies were evaluated (Table 2).

Overall, 36 patients (56%) met criteria for complete rituximab response, including 58% aged <18 years and 55% aged ≥18 years (*P* = .23). Response rates were not different in men versus women (64% [16/25] versus 51% [20/39]; *P* = .44). Although response was not significantly associated with the phase of ITP, the highest response rate was seen earlier in the ITP course: 73% (8/11) in newly diagnosed, 36% (5/14) in persistent, and 59% (23/39) in chronic ITP (*P* = .18). Response was not associated with the number of prior treatments (*P* = .13) or with response to prior treatment with IVIG or corticosteroids. Of those who responded to corticosteroids (29/62), 18 (62%) responded to rituximab. Response rate was similar in those with primary versus secondary ITP (53% [23/43] vs 62% [13/21]; *P* = .60). The most common type of secondary ITP was Evans syndrome (81%, 17/21). Among those with Evans syndrome, 59% (10/17) responded to rituximab. Fifteen patients with a complete rituximab response received additional ITP-directed pharmacotherapy >6 months after receiving rituximab.

In this cohort, the overall rituximab response rate (56%) was not significantly different between children and adults. Although the majority of patients had chronic ITP at the time of administration, many patients (39%) were treated earlier in the ITP course, within 12 months from initial diagnosis. A substantial number of patients (33%) treated with rituximab had secondary ITP. Despite the number of patients with secondary ITP, a comprehensive immunologic evaluation before administration of rituximab was not performed in most patients and was performed less often in adults than children. This might represent institution-specific practices or could represent a more general difference in how children and adults with ITP are evaluated and/or assessed before receiving rituximab. Given that the risks and response rate associated with rituximab may vary by type of secondary ITP, and that alternative targeted therapy may be available to a subset of patients with primary immune regulatory disorders, it is clear that guidance for pre-rituximab evaluation is needed.[11,15]

Identifying a potential underlying immunodeficiency is important given the associated risks of infection, hypogammaglobulinemia, and persistent B-cell depletion after rituximab in these conditions.[10-12] With more extensive testing, many patients with secondary ITP, including those with adult presentations, have been diagnosed with a monogenic immunodeficiency.[16,17] In these cases, targeted treatment may be available and more efficacious.[18] The higher frequency of pre-rituximab immunologic lab evaluation in children compared to adults suggests that there is variability in practice. Regardless of whether immunologic findings are associated with rituximab response, immunologic testing results inform risk of rituximab toxicity and can identify patients with immunodeficiencies, both of which may direct treatment. Understanding the correlation between immunologic labs and rituximab response and toxicity is limited by the current inconsistencies in immunologic testing before rituximab.

Identifying which patients will benefit from rituximab is challenging in the absence of available predictors. The complexity of shared decision making in selecting second-line treatments in ITP is emphasized in the 2019 American Society of Hematology adult ITP guidelines, which state that selection should be individualized on the basis of duration of disease, comorbidities, compliance, medication availability, cost, and patient values and preferences.[19] To aid in this decision, pre-treatment clinical and laboratory data that could reliably predict response to rituximab would be beneficial. In the longitudinal North American Chronic ITP Registry, response to

TABLE 1 Characteristics of children and adults treated with rituximab

Characteristics n (%) or median (range)	All patients (N = 64)	Age <18 y at time of first rituximab (n = 24)	Age ≥18 y at time of first rituximab (n = 40)	*P* value Fisher's exact or Wilcoxon rank-sum
Rituximab response[a]				
Nonresponse	22 (34)	6 (25)	16 (40)	.23
Partial response	6 (9)	4 (17)	2 (5)	
Complete response	36 (56)	14 (58)	22 (55)	
Sex				
Female	39 (61)	17 (71)	22 (55)	.29
Male	25 (39)	7 (29)	18 (45)	
Ethnicity				
Hispanic or Latino	13 (20)	7 (29)	6 (15)	.36
Not Hispanic or Latino	40 (63)	13 (54)	27 (68)	
Unknown	10 (16)	3 (13)	7 (17)	
Missing	1 (1)	1 (4)	0 (0)	
Race				
White	48 (75)	15 (62)	33 (82)	.13
Black	4 (6)	3 (12)	1 (2)	.14
Asian	2 (3)	1 (4)	1 (2)	>.99
Other	10 (16)	5 (21)	5 (12)	.48
Age at diagnosis, y	20.2 (0.9-83.2)	11.2 (0.9-16.8)	47.7 (2.9-83.2)	<.001
Age at first rituximab, y	27.3 (1.3-84)	12.1 (1.3-17.6)	52.6 (18.2-84)	<.001
Type of ITP				
Primary ITP	43 (67)	12 (50)	31 (78)	.03
Secondary ITP[b]	21 (33)	12 (50)	9 (22)	
Phase of ITP at the time of rituximab				
Newly diagnosed, <3 mo	11 (17)	3 (12)	8 (20)	.24
Persistent, 3-12 mo	14 (22)	8 (33)	6 (15)	
Chronic, >12 mo	39 (61)	13 (54)	26 (65)	
Number of different treatments given before rituximab	3 (17)	3 (16)	3 (17)	.10
Number of patients who received treatment prior to rituximab				
Corticosteroids	62 (97)	23 (96)	39 (98)	>.99
IVIG	44 (69)	21 (88)	23 (57)	.01
Romiplostim	23 (36)	5 (21)	18 (45)	.06
Eltrombopag	16 (25)	6 (25)	10 (25)	>.99
6-Mercaptopurine	16 (25)	13 (54)	3 (8)	<.001
Mycophenolate	8 (12)	5 (21)	3 (8)	.14
Splenectomy[c]	10 (16)	1 (4)	9 (22)	.08
IVIG response				
Nonresponse	13 (20)	6 (25)	7 (18)	.66
Partial response	12 (19)	7 (29)	5 (12)	
Complete response	18 (28)	7 (29)	11 (28)	
Unknown/missing	21 (33)	4 (17)	17 (42)	
Corticosteroid response				
Nonresponse	16 (25)	8 (33)	8 (20)	.62

(Continues)

TABLE 1 (Continued)

Characteristics n (%) or median (range)	All patients (N = 64)	Age <18 y at time of first rituximab (n = 24)	Age ≥18 y at time of first rituximab (n = 40)	*P* value Fisher's exact or Wilcoxon rank-sum
Partial response	14 (22)	5 (21)	9 (22)	
Complete response	29 (45)	9 (38)	20 (50)	
Unknown/missing	5 (8)	2 (8)	3 (7)	
Platelet count at diagnosis, 10^9/L	10 (0-102)	13.5 (2-84)	10 (0-102)	.15
Platelet count nadir, 10^9/L	5 (0-54)	5 (1-51)	4 (0-54)	.60
Platelet count before rituximab, 10^9/L	30 (1-549)	20 (1-117)	35 (1-549)	.03
ANA positive, ≥1:80	16 (25)	5 (21)	11 (28)	.77
DAT positive	8 (12)	0 (0)	8 (20)	.02
IgG testing obtained	54 (84)	20 (83)	34 (85)	>.99
Hypergammaglobulinemia[d]	4 (7)	0 (0)	4 (12)	.29
Hypogammaglobulinemia[e]	13 (24)	5 (25)	8 (24)	>.99
IgA testing obtained	54 (84)	20 (83)	34 (85)	>.99
Low IgA[f]	11 (20)	5 (25)	6 (18)	.73
B-cell lymphocyte subsets obtained	28 (44)	21 (88)	7 (18)	<.001
Low B-cell (CD19) number[g]	7 (25)	5 (24)	2 (29)	>.99

Abbreviations: ANA, antinuclear antibody; DAT, direct antiglobulin test; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin.

[a]Rituximab response: at least one platelet count >100 × 10^9/L within 6 months of the first dose of rituximab.

[b]Types of secondary ITP for children <18 y: Evans (n = 10), systemic lupus erythematosus (n = 1), autoimmune lymphoproliferative syndrome (n = 1), other (n = 1). Types of secondary ITP for adults >18 y: Evans (n = 7), rheumatologic diagnosis (n = 2), common variable immunodeficiency (n = 2).

[c]Median age of splenectomy: 49.2 y (range, 5.5-76.5).

[d]Hypergammaglobulinemia: IgG>2000 mg/dL.

[e]Hypogammglobulinemia: IgG<600 mg/dL.

[f]Low IgA: IgA<7 mg/dL.

[g]Low B-cell number: absolute CD19 <110 cells/μL.

corticosteroids and presence of secondary ITP were identified as strong correlates of response to rituximab.[8] In adults with primary ITP, age <40 years old and female sex were significantly associated with better long-term response to rituximab.[9] In contrast, in this cohort, there were not significant clinical or laboratory characteristics of rituximab response. The higher response rate seen when rituximab was given earlier in the disease course may reflect the higher likelihood of remission in those patients who are closer to diagnosis. This finding is consistent with trials demonstrating that rituximab treatment in adults with newly diagnosed ITP results in improved platelet responses at 6 and 12 months but unchanged long-term remission rates.[10]

Limitations of this study include those inherent to retrospective studies, such as missing and incomplete data for some patients, as well as inability to account for treatments or testing from other centers or prior to EMR development. ICD-9 and -10 codes were used to identify patients, so it is possible that some patients were missed. There may also be selection bias in terms of which patients received rituximab, particularly given the difference in immunologic testing by patient age, as some patients who underwent immunologic testing may have received an alternative treatment and/or had a change in diagnosis, and the response rate in the adult cohort may have been different if the same testing had been performed in the older cohort. This study did not use controls to compare rates of immunologic testing among patients with ITP who did not receive rituximab. Finally, this analysis included data from two large academic medical centers, which may not reflect practices at other treatment facilities.

In conclusion, this observational study describes the characteristics of adult and pediatric patients with ITP treated with rituximab at two tertiary ITP referral centers over the past 10 years. The overall rituximab response rate did not vary significantly between children and adults. Immunologic markers before rituximab treatment were not associated with rituximab response. Immunologic testing pre-rituximab and rates of diagnosis of secondary ITP significantly varied by age, suggesting that guidance is needed regarding pre-rituximab testing in patients with ITP.

TABLE 2 Likelihood of rituximab response by clinical and laboratory characteristics

Clinical/Laboratory characteristic n (%) or median (range)	N[a] (N = 64)	Rituximab responder (n = 36)	Rituximab nonresponder (n = 28)	*P* value Fisher's exact or Wilcoxon rank-sum
Sex				
Male	25	16 (64)	9 (36)	.44
Female	39	20 (51)	19 (49)	
Age				
<18 y at first rituximab	24	14 (58)	10 (42)	>.99
≥18 y at first rituximab	40	22 (55)	18 (45)	
Type of ITP				
Primary ITP	43	23 (53)	20 (47)	.60
Secondary ITP	21	13 (62)	8 (38)	
Phase of ITP at time of rituximab				
Newly diagnosed, <3 mo	11	8 (73)	3 (27)	.18
Persistent, 3-12 mo	14	5 (36)	9 (64)	
Chronic, >12 mo	39	23 (59)	16 (41)	
Number of different treatments given prior to rituximab	3 (1-7)	2 (1-6)	3 (1-7)	.13
Complete IVIG response	18	8 (44)	10 (56)	.23
Complete corticosteroid response	29	18 (62)	11 (38)	.79
ANA obtained	32	20 (62)	12 (38)	.45
ANA positive, ≥1:80	19	10 (53)	9 (47)	.79
DAT obtained	51	28 (55)	23 (45)	.76
DAT positive	8	4 (50)	4 (50)	.72
IgG level obtained	54	31 (57)	23 (43)	>.74
Hypergammaglobulinemia[a]	4	2 (50)	2 (50)	>.99
Hypogammaglobulinemia[b]	13	7 (54)	6 (46)	>.99
IgA level obtained	54	30 (56)	24 (44)	>.99
Low IgA level[c]	11	7 (64)	4 (36)	.74
B-cell lymphocyte subsets obtained	28	16 (57)	12 (43)	>.99
Low B-cell (CD19) number[d]	7	4 (57)	3 (43)	.65

Abbreviations: ANA, antinuclear antibody; DAT, direct antiglobulin test; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin.
Lab values correspond to the earliest available result chronologically.
[a]Hypergammaglobulinemia: IgG level >2000 mg/dL.
[b]Hypogammaglobulinemia: IgG level<600 mg/dL.
[c]Low IgA level: <7 mg/dL.
[d]Low B-cell number: absolute CD19 < 110 cells/μL.

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AUTHOR CONTRIBUTIONS

EMH, KH, HAS, and RFG designed the study, analyzed the data, and wrote the manuscript. LB performed the statistical analysis and edited the manuscript. All authors reviewed the final manuscript and agreed to its submission in its current form.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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