

## Research Article

# Patterns of Care and Association of Response with Rituximab among Patients of Immune Thrombocytopenia Purpura in a Rural Practice

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## Introduction

ITP results from antiplatelet antibodies targeting primary platelet glycoproteins such as GP IIb/IIIa. Production of cross-reactive antiplatelet antibodies by autoreactive B cells in response to infection and impaired expression of inhibitory Fc receptors have been implicated [1,2]. Beyond the effects on circulating platelets, these antibodies are also directed against platelet glycoproteins on the surface of megakaryocytes, inducing apoptosis-like programmed cell death and reducing platelet production [3-5]. In certain settings, such as inflammation, Antigen-presenting cells APCs create cryptic epitopes that can escape negative selection. Furthermore, the T cells observed are primarily against cryptic rather than native epitopes [6]. Supporting a role for APCs as critical cells in the development of ITP. In addition, patients with ITP demonstrate an increased Th1/Th2 ratio favoring autoreactive B-cell [7].

Treatment of ITP has evolved from blocking platelet clearance with corticosteroids, intravenous immunoglobulin (IVI g) or removing the site of clearance with splenectomy, to B and T cell modulation, as well as thrombopoietin agonists to boost platelet production. Several studies have examined whether more intensive dosing of steroids in newly-diagnosed ITP leads to more durable remissions. Although there has been some success with HD Dexamethasone [8,9] the role of B cell modulation with rituximab in improving sustained platelet response (SR) across different lines of treatment is unclear. Some studies demonstrate higher sustained response (SR) with the addition of rituximab to HD, 60%-76% compared to 30-36% with Dexamethasone alone [10-12] as well as improved responses. However, other studies fail to reproduce the composite end points of platelets  $>50 \times 10^9/L$ , reduction of significant bleeding or rescue treatment once standard treatment of HD Dexamethasone was

## Abstract

Immune thrombocytopenia (ITP) is a heterogeneous disorder of immune dysregulation of T and autoreactive B cells leading to the immune-mediated destruction of platelets due to the eventual loss of immune tolerance against platelet epitopes.

**Keywords:** Immune thrombocytopenia; Thrombocytopenia; Dexamethasone

stopped [13]. In this study, we look at responses in ITP patients in rural community setting receiving rituximab vs alternative therapies.

## Methods

A retrospective review of three hundred sixty-two patients with thrombocytopenia (ICD 9 287.5 and 287.31; ICD 10 D 69.6, D 69.3) seen between Jan 1990 to June 2016 across three rural community practices in southeastern NM was performed.

Patients with Secondary Non-immune thrombocytopenia due to chronic liver disease related to Alcohol, Hepatitis C, Cirrhosis, hypersplenism, leukemia, CLL, Lymphoma, and or drug-related thrombocytopenia were excluded from the statistical analysis N=88 (24%). Secondary Immune related thrombocytopenia that were included in secondary analysis were patients with ANA  $>1:640$  and or clinical features of collagen vascular disorders N=41 (11%). Fisher exact test was used to determine the association of treatment and response in both primary and secondary ITP. The International Working Group (IWG-2011) classification and criteria were used to assess response [14]. Sustained Response (SR) was defined as a platelet count of  $>50,000$  per cubic millimeter six months after treatment [8,14].

## Complete response (CR)

Platelet count  $\geq 100 \times 10^9/L$  and absence of bleeding.

## Partial response (PR)

Platelet count  $\geq 30 \times 10^9/L$  and at least 2-fold increase the baseline count and absence of bleeding.

**No response (NR):** Platelet count  $<30 \times 10^9/L$  or less than 2-fold increase of baseline platelet count or bleeding. Relapse was any platelet below  $50 \times 10^9/L$  or bleeding.

**Table 1:** Demographic and clinical baseline characteristics.

	Total Patients	Primary ITP
<b>Total Patients</b>	362 (100%)	233 (64%)
<b>Age At Diagnosis</b>		
≤ 60	171 (47%)	105(45%)
>60	191 (53%)	128(55%)
<b>Median (Range)</b>	61 (10-98)	63(10-98)
<b>Gender</b>		
Female	176 (49%)	121(52%)
Male	186 (51%)	112(48%)
<b>PLT On Diagnosis (Thousand)</b>		
<50	102(28%)	77(33%)
≥50	260(72%)	156(67%)
<b>Median (Range)</b>	90 (0-148)	90(0-148)
<b>Bone Marrow Biopsy Findings</b>		
Not Done	271(75%)	170(73%)
Negative	64(18%)	47(20%)
Positive	27(7%)	16(7%)

**Table 2:** Association of response to 1<sup>st</sup> line treatment and the medications received.

Among Primary ITP and Secondary Thrombocytopenia Patients Who Received 1<sup>st</sup> Line Treatment (n=131).

1 <sup>st</sup> Line Treatment Drugs Given	Response		p-value*
	Non-CR	CR	
<b>IVIG (n=26)</b>	11 (42%)	15 (58%)	0.15
<b>Prednisone (n=51)</b>	20 (39%)	31 (61%)	
<b>Dexamethasone (n=25)</b>	4 (16%)	21 (84%)	
<b>Rituxan (n=12)</b>	2 (17%)	10 (83%)	
<b>Other (n=17)</b>	5 (29%)	12 (71%)	
<b>Treatment with Steroid</b>			0.65
No (n=28)	10 (36%)	18 (64%)	
Yes (n=103)	32 (31%)	71 (69%)	

\*p-value based on Fisher's exact test

**Loss of CR**

Platelet count below 100×10<sup>9</sup>/L or bleeding (from CR).

**Persistent ITPs**

3-12-month duration. Different criteria are used to describe chronic ITP in different papers >6 months to >12 months. [14,15]. The protocol was approved and study in accordance with the IRB at Texas Tech University Health Sciences Center.

**Results**

Two hundred thirty-three patients (64%) had primary ITP 41 (11%) had secondary immune related ITP as described. The demographic and clinical baseline characteristics are outlined in (Table 1). Median age of diagnosis was 61 and median platelet on diagnosis was 90 (0-148). The median platelet count in patients <50 was lower at 77. One hundred seventy (73%) patients with primary ITP did not have a bone marrow biopsy, 63 patients (27%) did have bone marrow biopsy to confirm the diagnosis. Megakaryocytic

**Table 3:** Association of response with rituxan among primary ITP and secondary thrombocytopenia patients.

a. Response to 3<sup>rd</sup> Line Treatment (n=41).

Response to 3 <sup>rd</sup> Line Treatment	3 <sup>rd</sup> Line Treatment with Rituxan for ITP		p-value*
	No (n=27)	Yes (n=14)	
<b>Non CR</b>	5 (19%)	8 (57%)	0.017
<b>CR</b>	22 (81%)	6 (43%)	
<b>Non SR</b>	0 (0%)	5 (36%)	0.003
<b>SR</b>	26 (96%)	9 (64%)	

\*p-value based on Fisher's exact test

CR= Complete response

SR= Sustained response

b. Response to All Treatments (n=131).

Response to All Treatments Received	Ever Treated with Rituxan for ITP		p-value*
	No (n=84)	Yes (n=47)	
<b>Never achieved CR</b>	16 (19%)	6 (13%)	0.47
<b>Achieved CR</b>	68 (81%)	41 (87%)	
<b>Never achieved SR</b>	2 (2%)	3 (6%)	0.35
<b>Achieved SR</b>	82 (98%)	44 (94%)	

\*p-value based on Fisher's exact test

CR= Complete response

SR= Sustained response

hyperplasia was the most common diagnostic finding in primary ITP (n=15).

In the first line, one hundred forty-three ITP patients (52%) were followed by observation alone and 131 (48%) received treatment. Sixty-six patients (24%) received second line treatment and 41 (15%) patients received third line treatment. For those receiving treatment, Rituximab was used in 9% (12/131), 39% (26/66) and 34% (41/66) of first, second and third line treatments. For the whole ITP cohort (including treated and untreated patients), the CR was 45% (122/274); 39% (107/274) had no response (NR). For patients who received treatment, CR was achieved in 68% (89/131) in first line compared to 56% (37/66) in 2<sup>nd</sup> line and 68% (28/41) in third line treatment.

Among Primary and secondary ITP patients in 1<sup>st</sup> line (n=131) receiving IVIG in 1<sup>st</sup> line (n=26), CR was 58% (n=15); prednisone (n=51) CR rate was 61% (n=31); dexamethasone (Four dose protocol of high dose dexamethasone-HDD) had a higher than predicted CR rate of 84% (n=21/25) with Rituximab (n=12) the CR was 83% (p=0.15), also the use of steroid did not affect the CR rate (Table 2).

In first line use sustained response (SR) rates were higher in Rituximab group 92% (11/12) compared to the non-Rituximab group 78% (93/119), but not statistically significant (p-value=0.46). Similar trends were seen in the second line treatment. We noted higher CR/ SR rates in non- Rituximab group in the third line setting (Table 3A) with CR being 81% vs. 43% favoring the Non- Rituximab group (p=0.017) which comprised of thrombomimetic agents (n=8), and splenectomy patients (n=7) comprising 36.5% of the 3<sup>rd</sup> line treatment group. This group achieved a SR rate of 96% (26/27).

A total of 36% (47/131) ITP patients received Rituximab across multiple lines of treatment. Across all lines of treatment Rituximab was not associated with a higher CR against the Non-rituximab group (87% v/s 81%) (p=0.47) or SR (p=0.35) (Table 3B).

Out of 238 patients treated across three lines of therapy, 53 (22%) had some toxicity requiring treatment interruption or reduction, but most toxicities were mild. Toxicities with Rituximab were seen in 5/47 patients (10%) mostly limited to infusion reactions, anxiety, rash and fatigue. Only 1 case of sepsis was seen in association with only chronic steroid use.

## Discussion

Corticosteroids remain the cornerstone treatment for first line therapy of ITP. At least 30-80% of patients with ITP initially respond to corticosteroids [8,16,17] although most of these individuals relapse when steroids are tapered [8,18,19].

Some series report higher responses with Dexamethasone [17]. Several studies have suggested that intensive dosing of steroids and using HD Dexamethasone (HDD) in newly-diagnosed ITP leads to more durable remissions. Mazzucconi, et al. and Italian investigators in monocentric and multicentered GIMEMA thrombocytopenia working party observed that treatment of newly-diagnosed ITP with 4-6 cycles of dexamethasone given at two-week intervals led to relapse-free survival of 80-90% at 15 months. Long-term responses, lasting for a median time of 26 months (range 6-77 months) were 25 of 37 (67.6%) [18]. Cheng, et al. reported that treatment with a single course of dexamethasone (40 mg/day for four days) led to sustained responses (platelet count  $>50 \times 10^9/L$  at 6 months) in 50% of responders [8]. In another small, randomized study of 151 patients of ITP, a single course of high dose dexamethasone did not induce a greater percentage of sustained responses than standard doses of prednisolone [20].

In our analysis, we also included patients who received IVI g as is reflective of real world practice. This may explain our higher CR and SR. As a rescue medication, IVI g increases the platelet count in 60-80% of treated patients, often within days, and is effective in both non-splenectomized and splenectomized patients, although responses are usually of short duration (1-3 weeks). Our group prefers the convenience of a 1 gm/kg/day infusion for 1 or 2 days as previously studied [17,21]. A smaller sample may also be responsible for the differences. However, our initial responses with dexamethasone mostly correlate with HD Dexamethasone studies [8,9,18,19].

Rituximab is obviously an appealing choice because of its curative potential and relative safety compared to T-cell modulation which has wider immunosuppressive effects [22,23] smaller series experience [24] and because hematologists are familiar with its use in other settings. Four once-weekly intravenous infusions at 375 mg/m<sup>2</sup> induce CR in 44% of patients and an overall platelet count response in 62.5% of adults with ITP [13]. The lower CR rates in that study could be related to these patients being relapsed and refractory with a history of multiple relapses.

There has been a suggestion of a more complex mechanism for Rituximab than CD20<sup>+</sup> B-cell depletion. Intensification regimens using rituximab can cause reversal of Th1/Th2 ratios [25,26]. These findings are consistent with the hypothesis that auto antibodies in ITP develop as a consequence of T cell-dependent antigen-driven clonal expansion and somatic mutation [27]. Responding patient show restored numbers of Tregs as well as a restored regulatory function upon treatment with rituximab [25]. There is often delay between

B-cell depletion and platelet count response in most patients and it is unclear why some patients fail rituximab therapy in these studies. Our study suggested longer SR in earlier lines than in later lines but no statistical benefit compared to other treatments. Relatively poor long-term rates of sustained immune tolerance may be one of the reasons for lack of long term response to rituximab in our study particularly within the 3<sup>rd</sup> line setting compared to thrombomimetic and Splenectomy.

Another randomized trial investigating rituximab efficacy in previously untreated adult ITP patients demonstrated a higher sustained response rate at 6 months in patients that received the combination of Rituximab and dexamethasone (63% vs. 36%, n = 52, P <0.004); however, these differences were lost on longer follow up [11]. There was a higher incidence of infections in the patients treated with combined modality therapy.

In a study using Rituximab, splenectomy was deferred by 2 years in 40% of the patients and at 2 years with 33.3% (20/60) patients. [28] In our cohort 5 patients who received splenectomy after Rituximab infusion had their procedure delayed for a mean of 20.6 months (Range 3-65 months).

Patients with CRs generally persist at least 1 year; those with PRs usually relapse within 6 months [29]. In adults, the CR rate falls to approximately 20% by 2-5 years after a single 4-infusion course [28,30]. In one study children, did not relapse after 2 years from initial treatment whereas adults did [31,32]. Initial CR and prolonged B-cell depletion predicted sustained responses whereas prior splenectomy, age, sex, and duration of ITP did not. Hyperglycemia was the most common side effect requiring treatment interruption or reduction in 4.2% (10/238), Insomnia was seen in (5/238) 2%.

In our dataset, the use of rituximab across all lines of treatment was not associated with a higher CR or SR. Our higher than expected response rates with steroids may be due to inclusion of other intensification treatments like IVI g. We may have over treated some patients who may have undergone spontaneous remission given the higher mean platelet counts but captured others at a more advanced stage of illness especially those with secondary immune thrombocytopenia. Our trial did not specify a standard treatment, reflecting current practice variability in a real-world scenario. Our results suggest that the treatment effect with rituximab in the setting of new and relapsed disease may have been higher but not necessarily better than with HD Dexamethasone and/ or IVI g. An important distinction in our study is not just what modality to treat with but which ITP patients need intervention. Factors that underwrite management decisions include the extent of bleeding, comorbidities, complications of specific therapies like steroids or Rituximab, activity and lifestyle, planned interventions that increase bleeding risk etc.

Patient expectations and patient need for non-ITP medications that may create a bleeding risk is an important determinant especially in elderly for e.g. need for NSAIDs for pain and ASA/ Plavix for Cardiovascular risk reduction. Although a perpetual concern the actual bleeding risk is extremely small 0.0162 to 0.0389 cases per adult patient-year [33]. Treatment is rarely indicated in patients with platelet counts above  $50 \times 10^9/L$  in the absence of bleeding due to platelet dysfunction or another hemostatic defect, trauma, surgery [19].

We must consider variability in choice and duration of treatments, small sample size and retrospective nature. The use of Rituximab however is limited in real world rural practices especially in the first line setting possibly partly due to insurance denials and cost. In this study, additional considerations limit its use. Lack of FDA or European Medicines Agency for use in ITP is an important determinant. Although it is currently reimbursed for this purpose in case by case basis. Evidence-based guidelines offer a grade 2C recommendation for its use for patients who have failed corticosteroids, IVI g, or splenectomy [1,13,14]. Splenectomy may be more cost effective [34].

Intensifying therapy in later line was more successful with medications like romiplostim and splenectomy compared to rituximab achieving nearly a 96% SR. In our study 7 patients in third line that had romiplostim all had a CR except 1 who had a PR. After romiplostim no patient in our group received rituximab. Out of 14 romiplostim patients 4 patients had rituximab prior and mean time to treatment with romiplostim was 15 months (median 15.5 months).

Other ways to intensifying therapy in first line should be evaluated in prospective clinical trials like use of IVI g with or without the use of Rituximab and whether upfront intensive treatment avoids earlier recurrence needs to be further studied. This study included various treatment standards over the last 20 years. Our analysis reflects a realistic approach to using rituximab and other escalation regimens in the sequencing of ITP treatments protocols that recognizes wide variability of practices based on access to resources, physician preferences. It offers a unique reflection of patterns of care in a diverse rural setting instead of a large single center experience.

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