Low Dose Rituximab in Chronic ITP: Still an Option in Resource Limited Settings

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Abstract The etiology of ITP remains unknown but its pathogenesis consists of loss of tolerance to platelet antigens. There is a complex dysregulation of the immune system involving both the B cells and the T cells. Splenectomy is the standard second line option in steroid refractory chronic ITP patients. However, costs of surgery and reluctance for surgery in severely thrombocytopenic patients on part of surgeons are major obstacles in resource limited settings. Rituximab has been used in both the standard doses of 375 mg/m² and low doses of 100 mg/m² with similar results. We studied the utility of low dose Rituximab (@100 mg/m² weekly × 4 doses) in resource limited settings. Overall response, complete response (CR) and partial response (PR) rates were 47.6% (10/21), 33.3% (7/21) and 14.3% (3/21) respectively. Median time to response in patients achieving CR was 75 days (range 45–185 days) while in patients achieving PR it was 105 days (range 45–165 days). However, there was no significant difference between males and females achieving CR or PR. We also observed that patients who had earlier responded to any form of treatment were more likely to respond to Rituximab treatment. The cumulative relapse free survival (RFS) at 13 months was 78%. By giving lower dose, six times less than conventional dosing dose, we have been able to demonstrate cost effectiveness in our

study population. We were able to administer all the doses in day care without any major adverse events leading to further cost savings on in-patient care.

Keywords Immune thrombocytopenic purpura · Refractory · Rituximab · Low dose

Introduction

In last three decades Immune thrombocytopenic purpura (ITP) has seen not only change in nomenclature from idiopathic [1] to immune but also greater understanding of pathophysiology which has translated to discovery of newer therapeutic agents in this common disorder. Splenectomy is the standard second line option in steroid refractory chronic ITP patients [2, 3]. However, reluctance on part of surgeons for splenectomy in thrombocytopenic patients and the costs of surgery are major obstacles in resource limited settings. Rituximab, a chimeric anti CD20 monoclonal antibody by causing selective B cell depletion has emerged as an effective agent in management of chronic ITP [4]. Most of the studies have given Rituximab in same doses as are recommended for B cell lymphomas, i.e. 375 mg/m² every week for 4 weeks [4, 5]. However, very few dose finding and pharmacokinetic studies have been carried out in patients with autoimmune diseases [5]. In comparison to B cell lymphomas, B cell burden in ITP and other autoimmune diseases is very low, hence it has been hypothesized that dose of Rituximab required for B cell depletion in autoimmune disorders would be considerably low [6]. A lower dose also translates into reduced costs which is an important factor in the resource limited settings. In this study we report

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efficacy and safety of low dose Rituximab in patients of chronic ITP.

Patients and Methods

Twenty one patients of chronic ITP were included in this open label non comparative, single center, prospective study. Chronic ITP was defined according to earlier guidelines of American society of Hematology [2] which required duration of illness for more than one year from onset. The inclusion criteria were: age >12 years, severe ITP as defined by presence of bleeding symptoms requiring therapeutic intervention [7], corticosteroid dependence as defined by the need for ongoing or repeated doses administration of corticosteroids for at least 2 months to maintain a platelet count at or above $30 \times 10^9/L$ and/or to avoid bleeding [6], previous treatment with at least one line of therapy. Informed consent was obtained from all individual participants included in the study. Patients who were seropositive for HIV, HbsAg, HCV or pregnant were excluded. The study was approved by the Institutional ethics committee and written informed consent was obtained from patients. Patients' main characteristics are summarized in Table 1.

Treatment

Fixed dose of 100 mg of Rituximab was administered weekly (on day 1 of weeks 1, 2, 3 and 4). No other cytotoxic or immunosuppressive drugs were given concurrently with Rituximab. Patients with steroid dependency to maintain platelet count $>20,000/mm^3$ or active bleeding prior to Rituximab were allowed to continue steroids

during Rituximab administration. However, steroids were tapered off following initiation of Rituximab therapy and response was assessed following complete discontinuation of steroids. Premedication with oral paracetamol 500 mg and IV chlorpheniramine 10 mg was given to all study subjects. All doses were administered in day care setting.

Response Criteria

Response criteria were defined on basis of earlier studies [2, 7]. Response assessment was done by monitoring platelet counts every week for one month, then bi-weekly for 06 months and monthly thereafter. Response assessment was done only after complete discontinuation of steroid therapy. Also during each visit patients were assessed for any bleeding manifestation. Rituximab-related toxicity was assessed during the period of treatment and during the follow-up. Clinical and laboratory side effects were evaluated and graded according to the WHO scale. Complete response (CR) was defined as platelet count $>100,000/mm^3$ measured on two occasions 7 days apart and absence of bleeding. Partial Response (PR) was defined as platelet count $50,000\text{--}100,000/mm^3$. Overall Response (OR) was defined as either CR or PR. Non-responders (NR) were patients with less than PR. We also assessed time to response (TTR) which was defined as the time necessary to reach a platelet count of $>50,000/mm^3$. Relapse was defined in a patient who, after responding initially, experienced bleeding symptoms due to thrombocytopenia or platelet counts fell below $30,000/mm^3$. In such patients relapse free survival (RFS), defined as period between achievement of response to subsequent relapse was assessed.

Statistical Analysis

Cox proportional hazard regression analysis was used to assess whether response to low dose rituximab in patients with ITP was associated with age, gender, baseline platelet counts and duration of the interval between diagnosis and rituximab therapy. Results were considered statistically significant when $p = 0.05$. Graphs of relapse free survival (RFS) were achieved using the Kaplan–Meier method. Statistical analyses were performed in R statistical software [8].

Results

Accrual and Baseline Clinical Characteristics

Twenty one patients of chronic ITP were administered low dose Rituximab after informed consent. All 21 patients

Table 1 Main clinical and laboratory features of patients before Rituximab treatment

Patients	21
Median age, years (range)	36 (13–66)
Males/females	8/13
Median weight, kg (range)	60 (40–84)
Median surface area, m ² (range)	1.7 (1.4–2.1)
Diagnosis-Rituximab median interval, months (range)	24 (6–184)
Median platelet count before Rituximab, $\times 10^9/L$ (range)	10 (5–24)
Previous treatments	
Steroids alone	06
Steroids + IVIg	02
Steroids + anti-D	04
Steroids + dapsone	06
Steroids + splenectomy	03

included in the study completed the therapeutic program receiving the four infusions of Rituximab as scheduled with mean compliance of 100%. All doses of Rituximab were administered in day care centre. Median age, weight and baseline platelet counts were 36 years, 60 kg and $10 \times 10^9/L$ respectively. Table 1 summarizes the main clinical and laboratory baseline characteristics.

Response to Therapy

Overall response (OR), complete response (CR) and partial response (PR) rates were 47.6% (10/21), 33.3% (7/21) and 14.3% (3/21) respectively (Table 2). Median time to response (TTR) in patients achieving CR was 75 days (range 45–185 days) while in patients achieving PR it was 105 days (range 45–165 days). By Cox proportional hazard regression analysis there was no significant correlation in achieving a CR or PR between age (Hazard ratio 1.012 (0.95 CI 0.959–1.068) ($p = 0.657$) and 0.994 (0.95 CI 0.951–1.039) ($p = 0.777$) respectively), duration of disease prior to Rituximab administration or baseline platelet counts [Hazard ratio 1.001 (0.95 CL 0.991–1.012) ($p = 0.744$) and 0.9947 (0.95 CL 0.983–1.007) ($p = 0.378$) respectively].

There were 04 patients below 20 years of age. There was no statistical difference in response between patients above and below 20 years of age. On log rank analysis there was no significant difference between males and females achieving CR or PR ($p = 0.40$ and 0.27 respectively). On analyzing patients according to presence or absence of any previous response to any therapy, it was found that patients who had earlier responded to any form of treatment were more likely to respond to Rituximab treatment. On applying Fishers exact test this was statistically significant ($p = 0.01$). There was no statistically significant correlation between response to Rituximab and type of prior treatment.

Median follow up of our patients is 385 days (range 90–633 days). Out of 10 patients who achieved response 02 patients relapsed. 01 patient with CR relapsed after 09 months, while 01 patient with initial PR relapsed

after 03 months. Cumulative relapse free survival (RFS) at 13 months was 78% (Fig. 1). Patient who had relapsed following initial CR underwent splenectomy and achieved CR following the procedure while patient who relapsed after PR was started on dapsone and maintained stable platelet counts. Interestingly all three patients of post splenectomy relapse, who received low dose Rituximab, achieved CR. Overall all patients tolerated Rituximab infusions. Infusion related adverse events in form of chills and body aches were seen in 13/21 (61.9%) patients. These were seen only with first infusion and were manageable with steroids and anti histaminics.

Discussion

The etiology of ITP remains unknown but its pathogenesis consists of loss of tolerance to platelet antigens. This leads to a phenotype of accelerated platelet destruction and impaired platelet production. There is a complex dysregulation of the immune system involving both the B cells and the T cells. Antiplatelet antibodies most commonly directed against GpIb/IX and GPIIb/IIIa platelet antigens mediate accelerated clearance from the circulation in large part via the reticuloendothelial system. In addition, cellular immunity is perturbed and T cell and cytokine profiles are significantly shifted toward a type 1 and Th17 proinflammatory immune response. ITP patients also exhibit decreased numbers of CD4+CD25+ T-regulatory cells (Tregs), which function to down-regulate T-cell responses [9, 10].

The therapeutic mechanisms of Rituximab in chronic ITP include antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), direct apoptotic signaling, affect B cell homeostasis, disturbed T-cell activation and possible vaccinal effects [11]. Although, Rituximab is now an established agent in the management of Steroid resistant Chronic ITP, its optimal dose is yet not established.

Table 2 Response rates and outcome after Rituximab therapy

Response	Number	Percentage
Complete response (CR)	07	33.3%
Partial response (PR)	03	14.2%
Overall response (OR)	10	47.5%
Median time to response for complete response (CR), d (range)	75 (45–185)	
Median time to response for partial response (PR), d (range)	105 (45–165)	
Relapse rate	02/10 (20%)	
After CR	01/07 (14%)	
After PR	01/03 (33.3%)

Fig. 1 Relapse free survival (RFS) in ten patients achieving response after Rituximab treatment

Most of the studies have given Rituximab in same doses as are recommended for B cell lymphomas, i.e. 375 mg/m² every week for 4 weeks [2]. This has been done based on the assumption that the B-cell total mass is much less than in patients with lymphoma and, therefore, a reduced dosage of Rituximab might be sufficient for its therapeutic purpose, although there have been very few dose-finding and pharmacokinetic studies performed in autoimmune diseases [4].

In a systematic review, standard dose of Rituximab had overall response rate of 62.5% with CR of 43.6% [4]. However, treatment free response at 5 years are modest at 21% [12]. The RITP trial showed no reduction in the rate of long-term treatment failure with Rituximab compared to placebo. However, apparently longer duration of response and numerically higher response rates were seen with Rituximab [13]. The R-ITP 1000 study evaluated a fixed dose of 1000 mg of Rituximab on D1 and D15 in a similar refractory ITP scenario and found it to be having similar efficacy with an ORR of 44% as compared to the standard dose of Rituximab [14].

Three studies using low dose Rituximab have been published with largest study enrolling 48 patients [6, 15, 16]. Main data from these studies have been compared with our study in Table 3. We showed an overall response rate (ORR) of 47.5% which is lower than that reported by Zaja et al. in their study on 45 patients which was 60.5%. This could be explained by a median platelet count of $10 \times 10^9/L$ at the time of Rituximab administration in our study which is considerably lower in comparison to other studies using low dose Rituximab. Also, the median interval from diagnosis of chronic ITP to administration of Rituximab was 24 months (range 06 months to 184 months) in our study which is much longer than in other studies. It has been shown by Provan et al. that earlier administration of Rituximab improve response rates [17].

Kinetics of Response

Although response to low dose Rituximab has been shown to be associated with age [15], we did not find any such association. Patients who had prior response to any form of therapy are more likely to respond to low dose Rituximab. As has been reported earlier, kinetics of response to low dose Rituximab is different from what is seen with standard dose Rituximab. Median time to response (TTR) in patients achieving CR was 75 days (range 45–185 days) while in patients achieving PR it was 105 days (range 45–165 days). Longer TTR observed with low dose Rituximab may be the consequence of the slower kinetic of B depletion achievable with this schedule [18, 19]. All three patients who relapsed after splenectomy achieved CR with low dose Rituximab. Though the number is small, this may be an interesting subgroup of patients who may be having different kinetics of Rituximab in the absence of spleen leading to increased efficacy in this subgroup.

Relapse Free Survival

The RFS in our study at 13 months was 78%. This is in sharp contrast to what has been reported by Zaja et al. [16] who in their study observed a 12- and 24-month cumulative relapse-free survival of 61 and 45% respectively. Is this

Table 3 Main data from studies using low dose Rituximab (100 mg $\times$ 4) and comparison with results from this study

References	Patients	Initial OR (%)	Initial CR (%)	Median time follow-up (months)	Relapse rate (%)
Provan et al. [6]	7	57	57	7–14	0
Zaja et al. [15]	28	75	43	11	33
Zaja et al. [16]	48	60.5	39.5	18	55
Present study	21	47.5	33.3	13	20

difference related to differences in ethnicity of the population studied? In the absence of definite insight into the etiopathogenesis of chronic ITP, there are no easy answers. However, a longer follow up would have given a better delineation of the difference being observed.

Adverse Effects

Mild infusional reactions up to 50% with first dose of Rituximab and serious adverse infusion reactions at a rate of <1% is well known with standard doses of Rituximab. Zaja et al. [16] reported safer profile with low dose Rituximab in their study cohort with only one case of interstitial pneumonia. We observed a similar adverse effect profile with no infectious, hematologic or extra-hematologic complications being documented during follow-up. No case of interstitial pneumonia was seen in this study. Although infusional reactions are unlikely to be related to the total dose of Rituximab being administered, we observed no such reactions in our small study cohort.

Cost Effectiveness

High cost of biologicals has a major impact on the treatment option in a given patient in a resource limited setting like India. The median body surface area of the patients in this study was 1.7 m². Traditional dosing of Rituximab (375 mg/m² weekly × 04 doses) would have meant total dose of 2550 mg for each patient. By giving lower dose, six times less than conventional dosing dose, we have been able to demonstrate cost effectiveness in our study population. We were able to administer all the doses in day care without any major adverse events leading to further cost savings on in-patient care.

Conclusion

Chronic ITP is a difficult autoimmune disorder to treat with variable outcomes. Steroid dependence/refractory state effectively leaves us with splenectomy and Rituximab as the only options having a possibility of long term remission. In the absence of predictors of long term response to either of the options and the requirement of a major surgical intervention in the form of splenectomy and its attendant risks of OPSI and thrombosis, Rituximab offers a viable second line option. Although recent studies have shown low rates of long term remissions in chronic ITP with Rituximab [13], it will continue be a second line option till better drugs are available. Combinations of Rituximab with Dexamethasone [19] or TPO mimetics [20] have also failed to show any additional benefits in chronic ITP patients. Hence, low dose Rituximab with near similar

OR/CR rates as its standard dose will continue as a second line option due to its better side effect profile and cost effectiveness. An interesting finding which comes out from our study is its efficacy in refractory chronic ITP cases who have relapsed after splenectomy. This group of patients is known to be refractory to most of the drugs and have very limited therapeutic options at present. Though numbers are very small, excellent response rates seen in our study needs further evaluation in large scale studies in this subgroup of chronic ITP patients. We also observed that delay in institution of Rituximab may be associated with lower ORR. Although this will be required to be studied in a RCT setting, the current evidence including this study favors early use of Rituximab [17]. Major limitations of our study are small number of patients and non-comparative design.

Compliance with Ethical Standards

Conflict of interest Authors Dr. Rajan Kapoor, Dr. Rajiv Kumar, Prof. M. Mahapatra, Prof. Hara P. Pati and Dr. Suman Kumar Pramanik declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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