Is Low Dose Rituximab Combined with High Dose Dexamethasone Effective in Newly Diagnosed Immune Thrombocytopenia (ITP) in Adult Patients? Analysis of Results of a Prospective Study from Eastern India

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ABSTRACT

Introduction: Primary immune thrombocytopenia (ITP) in adults usually follows a chronic course. Rituximab (375 mg/m^2) was approved initially as second line therapy in chronic ITP. The present study aimed to evaluate the efficacy, safety and response duration with combined low dose Rituximab (100 mg fixed dose) and high dose Dexamethasone as frontline therapy in adult with newly diagnosed ITP.

Material and methods: The present prospective study, conducted over two years, included 22 patients. They were administered with intravenous infusion of Rituximab at a dose of 100 mg for four doses on day1, day8, day15 and day22. Pulse dose Dexamethasone tablet 40 mg given orally for four consecutive days (days1-4) in two weeks interval. Response evaluation done in terms of peripheral blood platelet counts and recorded as complete(CR), partial(PR), no response(NR) and overall response rate(ORR) as per the published guidelines. The data were analysed using appropriate statistical tools.

Results: At diagnosis, median platelet count was 7x10^9/L (range,1-18x10^9/L). On day30, after completion of fourth dose, 13 patients achieved CR(59.09%), 2 achieved PR(9.09%) and ORR was 68.18%. Seven (31.81%) were NR. Nine (69.23%) of 13 patients who achieved CR showed complete sustained response (CSR) at 24 weeks of follow-up. Overall, the combination therapy was well tolerated.

Conclusion: Frontline therapy with combinations of low-dose Rituximab and high-dose Dexamethasone was effective with sustained response and well tolerated in adults with newly diagnosed ITP.

Keywords: Adult Patients, Immune Thrombocytopenia, Newly Diagnosed, Low Dose Rituximab.

INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder where there is antibody and cell mediated destruction of platelets. According to the Western literature, it has the incidence of 30 cases per million annually.[1] There is spontaneous recovery in about 70% of cases in children with newly diagnosed ITP, but in adults, it usually follows a chronic course.[2] Corticosteroids (prednisolone) are the established frontline therapy in adults; 75% of patients show a rise in platelet count but, only 5-30% sustains remission. High dose Dexamethasone (40mg/dose) in short pulses every 2 weeks is effective in 85% cases with a relapse in 50% at six months.[3]

Rituximab, a chimeric anti-CD20 monoclonal antibody[4], was approved in 1997 for treatment of follicular B-cell lymphoma and since then studied in other autoimmune hematological diseases.[5] Rituximab @ 375mg/m^2 approved initially as second line therapy in chronic ITP, showed complete response in 57% cases of chronic adult ITP patients. Low dose Rituximab (100 mg) was used by Zaja F et al[6], had shown similar results as compared to the standard dose. Gomez-Almaguer D et al[7] had shown ORR of 90.5% and low incidence of relapse with low-dose Rituximab (100mg) and high-dose Dexamethasone as frontline therapy for ITP in adults. Zhou H et al[8] from China retrospectively analyzed the efficacy and safety of combination therapy in newly diagnosed ITP and shown promising results. Kapoor R et al[9] from India published data on low dose rituximab therapy in chronic ITP. There is scarcity of data in newly diagnosed cases especially from this part of the country. The present study aimed to evaluate the efficacy, safety and response duration of the combination therapy as first line therapy in new onset adult ITP cases with the objectives to evaluate response to the combination therapy as frontline in newly diagnosed adult ITP, to evaluate the complete sustained response with this regimen and to evaluate the safety profile.

MATERIAL AND METHODS

The prospective study was conducted in the Hematology Department of NRS Medical College & Hospital, Kolkata over two years from January, 2015 to December, 2016. During study period, total 306 adult ITP patients attended; after proper counseling only 25 adult patients were enrolled. Out of 25 patients, one had pregnancy and two detected Australia surface antigen positivity (HBsAg). Finally 22

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patients included in the study. The study was approved by the Institutional Ethical Committee

Inclusion Criteria:

1) Age >18 yrs,
2) Active symptomatic Disease,
3) Newly Diagnosed ITP,
4) Baseline Platelet count < $30x10^9$/l on two occasions.

Exclusion Criteria:

1) Active bacterial/Viral infections,
2) Pregnancy,
3) Concomitant malignant disease,
4) Connective tissue disorder,
5) Received Rituximab or any other treatment except prednisolone (not more than 7 days).

Parameters studied: Detail clinical history including bleeding manifestations, prior history of major illness, drug history taken. Complete hemogram with peripheral blood smear examination at presentation, then weekly up to day 30 during treatment period and after that monthly once for next six months, routine viral markers (HBsAg, Anti HCV, HIV, Hepatitis B core Antibody), serum ANA profile, fasting plasma glucose, liver function test, serum urea/creatinine done at baseline for each patient.

Treatment Plan: Patients were administered fixed dose of 100mg Rituximab as intravenous infusion as per prescribing information[10] after proper premedication with Injection Pheniramine, tablet Paracetamol (650mg) half an hour before starting infusion; given for four doses (day1, day8, day15 & day22) and Dexamethasone tablet 40 mg orally for four days (day1-4) in 2 weeks interval. All patients received prophylactic antiviral Acyclovir tablet 400mg twice a day and Tablet Co-trimoxazole DS weekly twice for Pneumocystis prophylaxis for 6 months as our institutional policy.

Criteria for response: As per recommendation of "ASH guideline of ITP 2011"[11]:-

Complete Response (CR)- Platelet count≥$100x10^9$/L measured in two occasions >7 days apart in the absence of bleeding

Partial Response (PR)- Platelet count≥$30x10^9$/L taken in two occasions >7 days apart or 2-fold increase from baseline in absence of bleeding.

No Response (NR)- Platelet count≤$30x10^9$/L or a less than 2-fold increase from baseline or presence of bleeding.

Complete sustained response (CSR)- Platelet count maintained, without additional therapy for 6 months.

Overall Response Rate (ORR)- Presence of either CR or PR.

Bleeding manifestations of patients evaluated according to the ITP Bleeding Scale (IBLS) comprised of 11 site-specific grades.[12]

Safety Profile and Side-effects: Safety profile and side effects evaluated according to the guideline of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[13]

STATISTICAL ANALYSIS

Data were entered in data sheet (Microsoft office excel version 2013) and analyzed using appropriate statistical tools. Statistical significance was assumed at p value of <0.05.

RESULTS

Patient characteristics: During the study period of two years, total 306 adult ITP patients attended [Figure 1]. After careful consideration of the inclusion criteria and proper counselling, only 25 could be enrolled in the study. Out of these 25 patients, one had pregnancy, another two were positive for Hepatitis B surface antigen and failed in the screening. Finally, 22 patients were included in the study. All 22 patients completed treatment protocol and they were followed up for at least 24 weeks.

Out of the 22 patients [Table 1], 14 were female (63.6%). Median age was 35 years (range, 19 to 65 years). Regarding clinical features, 15 patients (68%) had grade 1 and 7 patients (32%) had grade 2 bleeding manifestations according to ITP bleeding scoring system.[10] Sixteen patients (72.72%) had history of oral mucosal and gum bleeding, 3 had epistaxis (13.63%) and rest 3 patients (13.63%) had only skin manifestations like petechial and purpuric spots. Median duration of symptoms were 11days (range, 3-30 days). Majority of the patients (45.45%) had a bleeding history for last 6 to 15 days. Median platelet count at diagnosis was $7x10^9$/L (range, 1-$18x10^9$/L).

Two patients had type II diabetes mellitus and on medication and one patient had hypothyroidism and were on L-thyroxine during this study period. All patients evaluated thoroughly according to protocol and all relevant investigations were sent before initiating therapy. Only those who were treatment naive or took oral prednisolone not more than seven days as prior therapy were included in this study. Patients were administered intravenous infusion of Rituximab and oral tablet Dexamethasone as per treatment plan.

Response evaluation: Platelet counts checked weekly in each visit for consecutive four weeks and thereafter monthly once for 48 weeks for responders and at least 24 weeks for non responders (NR).

As shown in Figure 2, after completion of first dose of Rituximab, on day 8, total 6 patients (27.27%) achieved CR, one achieved PR (4.54%) and rest 15 showed NR (68.18%). After completion of 2nd dose, on day 15, total 9 patients achieved CR (40.9%), 2 achieved PR (9.09%) and rest 11 showed NR (50%). After completion of 3rddose, on day 22, total 9 patients achieved CR (40.9%), 4 achieved PR (18.18%) and rest 9 showed NR (40.9%). After completion of fourth dose, on day 30, total 13 patients achieved CR (59.09%). Another 2 patients achieved PR at day 30 (9.09%); the overall response was 68.18%. Seven patients (31.81%) were NR and they received other form of medications for their bleeding manifestations [Figure 3]

Time to achieve CR after starting of treatment: Out of all 13 patients who achieved CR, six patients (46.1%)

achieved CR at day8 after first dose of Rituximab and first cycle of Dexamethasone, three patients (23.03%) responded after second dose of Rituximab at D15; rest 4 patients (30.76%) after fourth dose of Rituximab and second cycle of Dexamethasone at day28. Two patients achieved PR at day28.

Follow-up: All 15 patients who achieved either CR or PR were followed up for median follow up period of 38 weeks (range, 24-48 weeks). None of these 15 patients experienced any bleeding manifestations during this follow-up period and they had not received any other medication for ITP. Seven patients who were NR also followed up for at least 24 weeks for any adverse effects. They also received other form of medications for ITP [Figure 3]. Nine (69.23%) out of 13 patients who achieved CR showed complete sustained response even after 24 weeks. Four patients (30.76%) who initially achieved CR showed drop in platelet count after 24 weeks without any bleeding manifestation and reverted back to PR (they were followed up and were maintaining as PR (there were no need for other medications for these patients till last follow up). Platelet count (at different timeframe) of the 13 patients who achieved CR is shown in Figure 4.

Adverse effects: Overall, combination therapy with low dose Rituximab and high dose dexamethasone was well tolerated. There was no infusion related toxicity with low dose Rituximab infusion. Adverse effects seen in 7 (31.8%)

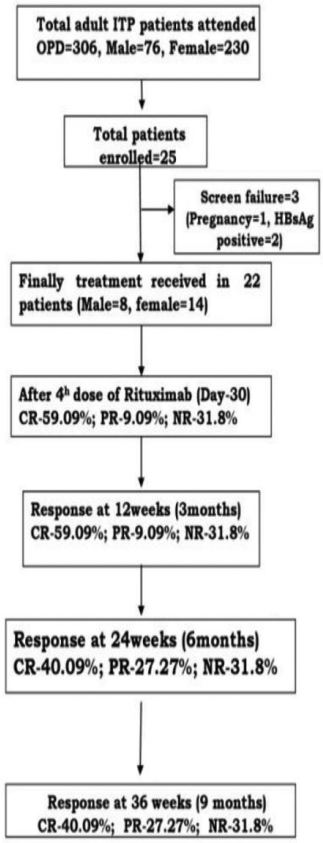

Figure-1: Consort diagram of the study populations showing the recruitment details of the cases and outcome.

Patients, n	22
Median age, years (range)	35 (19 – 65)
Male/female	14/8
Median platelet count at presentation, x 10^9/L (range)	7 (1 - 18)
Median duration bleeding symptoms, days (range)	11 (3 - 30)
Bleeding grade:- Grade I, n (%)- Grade II, n (%) -	 15 (68%), 7 (32%)
Site of bleeding:- Gum bleeding, n (%)- epistaxis, n (%)- Skin bleed, n (%)-	 16 (72.72%), 3 (13.63%), 3 (13.63%)
Comorbidities:- type II diabetes mellitus hypothyroidism	 2 (9.0%), 1 (4.5%)

Table-1: Demographic, clinical and laboratory features of the patients included in the study

Studies	Drugs used	Dosage	CR	PR	NR	ORR	CSR
Zaja F et al[6] N=37	Rituximab (wkly for 4 wks)	375 mg/m^2	54%	19%	27%	73%	49% at 22 wks
Li Z et al[16] N=32	Rituximab (wkly for 4 wks) + Dexa (d1-4)	100mg + 40mg PO	48.4%	19.4%	19.4%	67.7%	77.4% at 12 months
Gomez-Almaguer D et al[7] N=21	Rituximab (wkly for 4 wks) + Dexa (d1-4)	100mg + 40mg PO	81%	9.5%	9.5%	90.5%	94.1% at 6 months
Present Study, N=22	Rituximab (wkly for 4 wks) + Dexa (d1-4) & (d15-18)	100mg + 40mg PO	59%	9%	32%	68%	69.2% at 9 months

Table-2: Comparison between studies which used Rituximab as front line therapy in newly diagnosed ITP.

out of 22 patients. Two patients (9.09%) who were diabetic and on oral hypoglycaemic drugs showed rise in blood sugar level during treatment and required insulin administration.

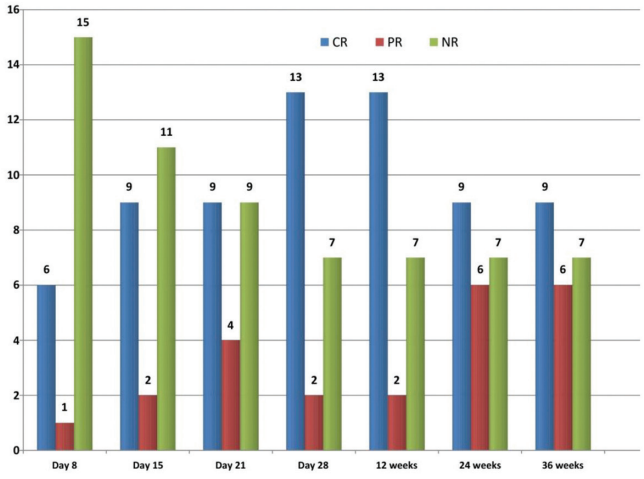

Figure-2: Clinical response of the patients (n=22) at different time frame [CR= complete response, PR= partial response, NR= no response].

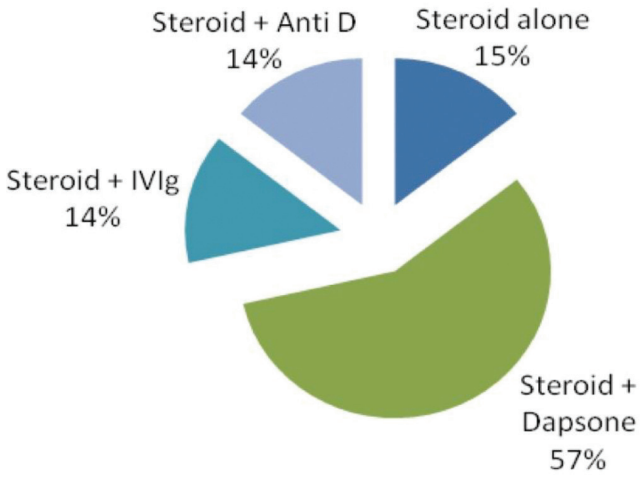

Figure-3: Detailed account of therapy given to the non-responders (n=7) who received other form of medications.

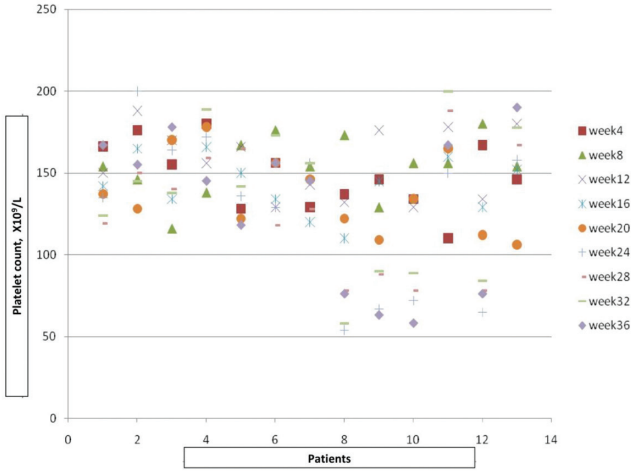

Figure-4: Platelet count of the patients (n=13) who achieved and sustained complete remission at diagnosis and follow up through 36 weeks.

Blood glucose level was controlled with insulin; discontinued after D30 and continued with oral hypoglycaemic drugs as before. Three patients developed mild gastrointestinal (GI) adverse effects (CTCAE grade1). Two complained of mild diarrhoea during treatment which subsided of its own. One patient developed nausea and heartburn during second week; treated with proton pump inhibitors and prokinetic agents and responded well. Two patients developed severe adverse effects requiring hospitalisation; one presented with severe abdominal pain, vomiting and abdominal distension after 2 months of completion of treatment, further evaluated in the surgery department and diagnosed as sub acute intestinal obstruction. He was finally diagnosed as intestinal tuberculosis, started with anti-tubercular drugs and completed it without further complications. Another patient developed cough, expectoration and respiratory distress after 4 month of completion of treatment. On evaluation it was found that he is having consolidation in both lungs- Computer tomograpgy (CT) scan guided fine needle aspiration was done which showed fungal hyphae. He was started with injection amphotericin in standard dosage and later changed to oral voriconazole, continued for two months until repeat CT scan revealed resolution of all the lesions.

DISCUSSION

For more than 50 yr, corticosteroids are used as first line treatment for ITP. Despite of high initial response/efficacy, in most cases, platelet count drops subsequently and requires additional or alternative therapy. Long term therapy with steroids even at lower doses is associated with several known side effects. Recommended first line therapies for ITP are corticosteroids, intravenous immunoglobulin (IVIG) and Anti-D.[11] Rituximab was approved and licensed in 1997 for the treatment of follicular B-cell lymphoma and also studied in various other autoimmune haematological disorsers including acquired hemophilia, thrombotic thrombocytopenic purpura, autoimmune hemolytic anemia, and ITP.[5] García-Chavez J et al[14] treated chronic and refractory ITP with rituximab (375 mg/m2) and reported CR of 28% and sustained response of 67%. Zaja F et al[6] first used low-dose Rituximab (100mg) as salvage therapy in previously treated symptomatic ITP; ORR and CR were achieved in 21/28(75%) and 12/28(43%) patients respectively. After median follow-up of 11 months (range, 3-18), 33% patients relapsed; 3 required further treatments. Gomez-Almaguer D et al[7] had shown CSR 76.2% with low dose Rituximab and high dose of Dexamethasone in treatment of new onset adult ITP. Zhou H et al[8] from China in 2019 reported 18 patients with CSR of 83.3% and 61.5% at 6 months and 12 months with a cumulative relapse-free survival at 12-month of 69.3%; adverse effects reported in 11.1%. Kapoor R et al[9] from capital city of India used low dose rituximab therapy in chronic ITP; had shown it's effectiveness in terms of ORR/ CR compared to other available options with better side effect profile and thus very important alternative option in resource constraint countries.

In the present study, 14/22(63.6%) were female; median

age 35 years (range,19-65 years); most were in the age group of 18-25 years (36.36%). Terrell DR et al[15] in their study on epidemiology of ITP described that in adults female prevalence of ITP in west is nearly double than male. Our study corroborated with their findings of female preponderance. Median platelet count at diagnosis in the present study was $7x10^9$/L (range, 1-$18x10^9$/L). After completion of fourth dose of Rituximab, at day 28, the CR, PR and OR was 59.09%, 9.09% and 68.18% respectively. Seven patients (31.81%) were non responders and received other form of medications for their bleeding manifestations. Gómez-Almaguer D et al[7] in the similar study done earlier had shown CR, PR and ORR at day 28 of 76.2%, 14.3% and 90.5% respectively. Li Z et al[16] studied with low-dose Rituximab and glucocorticoids for treatment of ITP patients; randomized sixty-two patients into control (glucocorticoids) and experimental (glucocorticoids + rituximab) groups. Both groups received dexamethasone 40 mg/day on days1-4; the experimental group in addition received Rituximab 100 mg on day7, day14, day21 and day28. ORR at day 28 was similar in both groups (experimental group vs. Control group: 80.6% vs. 74.2%, p=0.938). The ORR (68%) in the present study was lower than studies by Li Z et al[16] (80.6%) and Gómez-Almaguer D et al[7] (90.5%). This may be due to the genetic heterogeneity and different drug response in our populations.

In the present study, nine (69.23%) out of 13 patients (who achieved CR) showed complete sustained response (CSR) at 24 weeks (6 months) of follow-up. Gómez-Almaguer D et al[7] showed CR and CSR of 76.2% after 6 months of median follow-up. Zaja F et al[6] reported CSR of 63% at month 6 was with Rituximab 375 mg/m2 weekly for 4 wks. Li Z et al[14] reported CSR of 77.4% with Rituximab 100 mg weekly for four weeks. Comparison between studies which used Rituximab as front line therapy in new onset ITP are shown in the table 2.

Khellaf M et al[17] in their largest prospective study reported lasting response in 39% cases on median follow-up of 24 months with cumulative incidence of infections in 2.3 per 100 patient-years. Arnold D et al[18] reported ORR in 62.5% of adults with ITP; noted significant toxicities, including death in 2.9% of cases. Provan D et al[19] in a retrospective analyzed data from 11 patients with various autoimmune cytopenias (who failed to respond to conventional treatments and received Rituximab-100 mg weekly for 4 weeks); CSR achieved in 4/7 patients with idiopathic thrombocytopenic purpura and in 1/7 patient with autoimmune pancytopenia. They did not report single incident of infusion related toxicity. Schweizer C et al[20] used Rituximab in refractory and relapsed ITP and reported that it was effective and well tolerated; however, response duration was short, only one fifth of patients had long-lasting remission.

In the present study, combination therapy was well tolerated; not a single episode of infusion related toxicity. Two (9.09%) patients lost their glycemic control during treatment and required insulin therapy; after completion of treatment they became euglycaemic and insulin was stopped. Arnold DM et al[18] used standard dose of Rituximab and found more infusion related toxicities and incidence of infections. Overall, in comparison to standard dose Rituximab (375mg/m2), low dose Rituximab (100mg) is having similar efficacy and better side effect profile. The inherent limitation of this study is small sample size and limited period of observation and these findings should be corroborated with randomised control trials with large number of sample size.

CONCLUSION

Combination frontline therapy with low-dose Rituximab and high-dose Dexamethasone for adults with newly diagnosed ITP was effective, well tolerated and showed sustained response.

REFERENCES

1. Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database [published correction appears in Br J Haematol. 2009; 147(1): 157]. Br J Haematol. 2009; 145: 235–244.
2. George JN, el-Harake MA, Raskob GE. Chronic idiopathic thrombocytopenic purpura. N Engl J Med 1994; 331: 1207–1211.
3. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. Mayo Clin Proc 2004; 79: 504–522.
4. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83: 435–45.
5. Dierickx D, Delannoy A, Saja K, Verhoef G, Provan D. Anti-CD20 monoclonal antibodies and their use in adult autoimmune hematological disorders. Am J Hematol 2011; 86: 278–291.
6. Zaja F, Battista ML, Pirrotta MT, Palmieri S, Montagna M, Vianelli N, et al. Lower dose rituximab is active in adults patients with idiopathic thrombocytopenic purpura. Haematologica 2008; 93: 930–933.
7. Gómez-Almaguer D, Tarín-Arzaga L, Moreno-Jaime B, Jaime-Pérez JC, Ceballos-López AA, Ruiz-Argüelles GJ, et al. High response rate to low-dose rituximab plus high-dose dexamethasone as front line therapy in adult patients with primary immune thrombocytopenia. Eur J Haematol 2013; 90: 494-500.
8. Zhou H, Liu L, Shu X, Wang X, Song Y. Clinical Efficacy and Safety of High-Dose Dexamethasone Plus Low-Dose Rituximab as First-Line Therapy in Newly Diagnosed Primary Immune Thrombocytopenia. Indian J Hematol Blood Transfus. 2019; 35: 507–512.
9. Kapoor R, Kumar R, Mahapatra M, Pati HP, Pramanik SK. Low Dose Rituximab in Chronic ITP: Still an Option in Resource Limited Settings. Indian J Hematol Blood Transfus. 2017;33:568–573.
10. RITUXAN® (rituximab) full Prescribing Information, Genentech, Inc. 2016; 1 DNA Way South San Francisco, CA 94080-4990; US License Number 1048.
11. Neunert C, Lim W, Crowther M, Cohen A, Solberg Jr L and Crowther MA. ASH guideline of ITP 2011. Blood 2011; 117: 4190-4207.

12. Rodeghiero F, Michel M, Gernsheimer T, Ruggeri M, Blanchette V, Bussel JB, et al. Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group: Blood 2013; 121: 2596-606.
13. U.S. Department Of Health And Human Services. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).
14. Garcia-Chavez J, Majluf-Cruz A, Montiel-Cervantes L, García-Ruiz EM & Vela-Ojeda J. Rituximab therapy for chronic and refractory immune thrombocytopenic purpura: a long-term follow-up analysis. Ann Hematol 2007; 86: 871–7.
15. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. Am J Hematol 2010; 85: 174- 80.
16. Li Z, Mou W, Lu G, Cao J, He X, Pan X, et al. Low-dose rituximab combined with short-term glucocorticoids up-regulates Treg cell levels in patients with immune thrombocytopenia. Int J Hematol 2011; 93: 91–8.
17. Khellaf M, Charles-Nelson A, Fain O, Terriou L, Viallard JF, Cheze S, et al. Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients. Blood 2014; 124: 3228-36.
18. Arnold DM, Heddle NM, Carruthers J, Cook DJ, Crowther MA, Meyer RM, et al. A pilot randomized trial of adjuvant rituximab or placebo for non-splenectomized patients with immune thrombocytopenia. Blood 2012; 119: 1356–1362.
19. Provan D, Butler T, Evangelista ML, Amadori S, Newland AC, Stasi R. Activity and safety profile of low-dose rituximab for the treatment of autoimmune cytopenias in adults. Haematologica 2007; 92: 1695–98.
20. Schweizer C, Reu FJ, Ho AD, Hensel M. Low rate of long lasting remissions after successful treatment of immune thrombocytopenic purpura with Rituximab. Ann Hematol 2007; 86: 711-17.

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