International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Review Article

Rituximab Treatment in New and Refractory Thrombotic Thrombocytopenic Purpura (TTP) Patients: A Review

S P Bhat*, S Z Rahman

Department of Pharmacology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, UP, India.

ABSTRACT

Introduction: TTP is a rare but serious disease characterized by the development of von Willebrand factor (vWF)-platelet rich hyaline thrombi in the arterioles and capillaries due to deficiency of ADAMTS13 - A Disintegrin and Metalloproteinase with a ThromboSpondin type 1 motif, member 13. Rituximab is a chimeric monoclonal antibody against CD20 that has been successfully used in autoimmune diseases including TTP. But, there is no standardized regimen governing the use of Rituximab in TTP. Hence, this review focuses on the various regimens of Rituximab and the concerns with formulating standard guidelines for the treatment of TTP.

Material and methods: An extensive literature search was conducted using search engines such as Pubmed, Embase and Google scholar on the use of Rituximab in TTP. 50 case reports (19 male, 31 female) fulfilling the diagnostic criteria of TTP as per the BJH Guidelines aged between 11-77 years were analysed for use of Rituximab in new-onset and refractory TTP cases. The criteria for comparison were attainment of remission, time to remission, duration of remission and occurrence of relapses/failure.

Results: It was found that 100% new-onset cases and 84.61% refractory cases of TTP achieved remission when started on Rituximab. The time to remission with Rituximab was estimated to be between 7-14 days in 46.15% in new-onset cases and 83.33% among refractory TTP cases. The duration of remission noted during follow-up was 11-20 months in 31.57% new-onset and 45.45% refractory TTP cases upon commencement of Rituximab. The number of relapses and failure rates were higher among the female population.

Conclusions: Rituximab proved beneficial in terms of faster attainment and longer duration of remission, fewer relapses and failures, more so, in new-onset cases. Large clinical trials are required to reach a consensus among practitioners for the therapy of TTP.

Keywords: Rituximab; TTP; New-onset; Refractory; Failure.

***Correspondence to:**

Dr. Sangeeta P Bhat
Ex-Resident, Department of Pharmacology,
Jawaharlal Nehru Medical College,
Aligarh Muslim University, Aligarh, India.

Article History:

Received: 04-06-2016, **Revised:** 16-06-2016, **Accepted:** 14-07-2016

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2016.2.4.001	

INTRODUCTION

TTP is a rare but serious disease characterized by the development of von Willebrand factor (vWF)-platelet rich hyaline thrombi in the arterioles and capillaries. It affects the brain, heart, pancreas, kidney and other organs.[1] Under normal conditions, increased platelet aggregation is prevented by cleavage of the vWF multimers by a vWF-cleaving protease (ADAMTS13 - A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13).[2] There are 2 types of TTP – Hereditary TTP, the rarer form occurring due to mutations in the ADAMTS13 gene and Acquired TTP, the more common form due to production of auto-antibodies (mostly IgG type).

As per the British Journal of Haematology (BJH) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies,[3] new-onset TTP cases are defined as those having their first episode and refractory TTP cases are those with persistent thrombocytopenia after a total of 7 plasma exchange procedures. Initially, plasma exchange was considered to be the mainstay of treatment for TTP but, a significant subset of patients is found to be non-responsive to plasma exchange.[4]

Rituximab is a chimeric monoclonal antibody against CD20 that depletes B cells in the circulation and lymphoid tissues. It is primarily used in the treatment of CD20-positive lympho-proliferative disorders.[5] It has also been used successfully in patients with immune thrombocytopenic purpura and other types of autoimmune diseases.[6-21] The proposed mechanism of action of Rituximab is by the clearance of CD20-positive B cells that produce inhibitory anti-ADAMTS13 autoantibodies. Thus, the use of Rituximab has been investigated by numerous clinicians independently & concurrently with other therapies.

Numerous case reports have been published with regard to the use of Rituximab in new-onset and refractory TTP cases, inspite of which there is a deficit of clear guidelines for the treatment of this rare, but, life-threatening condition. Hence, the aim of this study: firstly is to review the various regimens of Rituximab in new-onset and refractory TTP cases, secondly to analyze the time to attain remission and duration of remission with various Rituximab regimens, thirdly to compare the failure and relapse rates post-Rituximab treatment, and lastly to summarize the obstacles in designing guidelines for TTP.

METHODS

Selection of cases

An extensive literature search was done through PubMed (Medline), Google scholar and Embase search engines on the use of Rituximab in TTP. 50 case reports (19 male, 31 female) fulfilling the diagnostic criteria of TTP as per the BJH Guidelines (Scully et al, 2012)[3] aged between 11-77 years were analysed. They were categorized into new-onset TTP cases - 24 (14 female, 10 male) and refractory TTP cases – 26 (17 female, 9 male) as mentioned in Tables 1 and 2 respectively.

In all regimens, Rituximab (375mg/m²) was administered by i.v. infusion weekly. Complete remission was defined as achievement of normal platelet count (>150 x 10^9/l). Relapse was defined as recurrence of TTP after a remission and failure was defined as inability to achieve normal platelet counts.

Criteria for comparison

Observations were made with respect to attainment of remission, time to remission, duration of remission, occurrence of relapses/failure and the findings were tabulated.

Data analysis

Data is expressed as Mean±S.D. wherever applicable and the results are expressed as percentage of the number of cases offered that regimen.

Table 1: Characteristics of patients with New-onset TTP.

Study	Case no.	Age (y)/ Sex	Older treatment	Concurrent therapy	Rituximab treatment (weeks)	Remission after Rituximab
Mak[30]	1	30/M	1, 2, 3	1, 2, 4	8	Yes
Chemnitz[2]	1	39/F	1, 2, 3	2	4	Yes
	2	37/F	1, 2, 3	2	2	Yes
	3	36/F	1, 2	1, 2	2	Yes#
	4	57/M	1, 2	-	4	Yes
	5	34/F	1, 2	-	4	Yes
Koulova[31]	1	40/M	1, 2, 3	-	4	Yes
Kameda[32]	1	26/F	1, 2	-	2	Yes
	2	38/F	1, 2, 3	-	2	Yes
Iioka[4]	1	40/F	1, 2, 3	-	4	Yes
	2	72/M	1, 2	3	4	Yes
	3	62/M	1, 2	-	4	Yes
Albaramki[33]	1	15/F	1, 2	1, 2, 3	4	Yes
Scully[34]	1	46/M	1, 2, 3	1, 2	4	Yes
	2	56/F	1, 2	-	4	Yes
	3	33/F	1, 2, 3	1, 2	4	Yes
	4	31/M	1, 2	1, 2	4	Yes
Kuppachi[35]	1	43/M	1, 2	1, 2	4	Yes
Magalini[36]	1	25/M	1, 2	1, 2, 3	4	Yes
Ozolugu[37]	1	22/F	1, 2, 3	1, 2	4	Yes
Millward[38]	1	20/F	1, 2	1, 2	1	Yes
Lombardi[39]	1	45/F	1, 2	1, 2, 3	NA	Yes
	2	44/F	1, 2	1, 2, 3	NA	Yes
	3	26/M	1, 2	1, 2, 3	NA	Yes

Treatment prior to Rituximab – 1, Plasma exchange; 2,Corticosteroids; 3, Immunosuppressants; Treatment concurrent with Rituximab – 1, Plasma exchange; 2,Corticosteroids; 3, Immunosuppressants; 4, Splenectomy; NA, Data not available; M, Male; F, Female; #, Remission followed by relapse.

RESULTS

Regimens in TTP

Several combinations of treatments are used before or concurrently with Rituximab as mentioned in Table 1 for new TTP cases and Table 2 for refractory TTP cases. Common modes of therapy are plasma exchange, corticosteroids, immunosuppressants and splenectomy. Rituximab has been tried for a period of 1, 2, 4 and 8 weeks in new-onset cases and 2, 4, 5, 6 and 8 weeks in refractory cases.

Attainment of remission in new-onset and refractory TTP cases upon commencement of Rituximab

On beginning Rituximab, all 24 out of 24 (100%) new-onset cases achieved remission as shown in Table 1 while 22 out of 26 (84.61%) refractory cases attained normal platelet counts as shown in Table 2. Among the 26 refractory cases, 11 patients had already been splenectomised, data of 4 patients was not available, while the rest of the 11 patients started on Rituximab, did not require splenectomy to achieve remission.

Table 2: Characteristics of patients with Refractory TTP.

Study	Case no.	Age (y)/ Sex	Older treatment	Concurrent therapy	Rituximab treatment (weeks)	Remission after Rituximab
Gutterman[40]	1	54/F	1, 2, 3, 4	1, 2	8	Yes
	2	62/F	1, 2, 3, 4	-	8	Yes#
	3	40/F	1, 2, 3, 4	-	4	No
Tsai[24]	1	36/F	1, 2, 3, 4	-	8	Yes
Yomtovian[41]	1	30/F	1, 2, 3, 4	1, 2	8	Yes
Ojeda[42]	1	25/F	1, 2	3	6	Yes#
Koulova[31]	1	45/M	1, 2, 4	1, 2	5	Yes
Zheng[43]	1	42/F	1, 2, 3	1, 2, 3	4	Yes
Iioka[4]	1	77/M	1, 2, 3	1, 2	4	Yes
Ahmad[44]	1	56/F	1, 2, 3	1, 2	4	No
	2	61/F	1, 2, 3	1, 2	4	No
	3	53/M	NA	1, 2, 3	2	Yes
	4	57/M	1, 2	1, 2, 3	4	Yes
Ling[45]	1	25/F	1, 2, 3	1, 2, 3	4	No
	2	55/F	NA	1, 2	4	Yes
	3	41/M	NA	1, 2	4	Yes
	4	44/F	NA	1, 2	4	Yes
Jayabose[46]	1	11/F	1, 2, 3	-	4	Yes
Kosugi[47]	1	69/M	1, 2, 3, 4	-	4	Yes
Reddy[48]	1	43/M	1, 2, 3, 4	1, 2	4	Yes
Fakhouri[49]	1	42/F	1, 2, 3	1, 2	4	Yes
	2	21/F	1, 2, 4	1, 2	4	Yes
	3	36/M	1, 2, 3, 4	1, 2	4	Yes
	4	40/M	1, 2, 3	1, 2	4	Yes#
Stein[50]	1	37/F	1, 2, 3, 4	1, 2, 3	4	Yes
Patino[51]	1	41/F	1, 2	1, 2	4	Yes#

Treatment prior to Rituximab – 1, Plasma exchange; 2,Corticosteroids; 3, Immunosuppressants; Treatment concurrent with Rituximab – 1, Plasma exchange; 2,Corticosteroids; 3, Immunosuppressants; 4, Splenectomy; NA, Data not available; M, Male; F, Female; #, Remission followed by relapse.

Table 3: Time to attain remission in new-onset and refractory TTP cases after commencement of Rituximab treatment.

New-onset cases of TTP						
Duration of Rituximab treatment	**Number of cases (Total = 24)**	**Cases with available data (Total = 13)**	**Time to attain remission**			
			< 7days (Total = 1)	**7-14 days (Total = 6)**	**15 -40 days (Total = 4)**	**>40 days (Total = 0)**
1 week	1	0	-	-	-	-
2 weeks	4	3	-	2	1	-
4 weeks	15	8	1	4	3	-
8 weeks	1	1	-	-	1	-
Refractory cases of TTP						
Duration of Rituximab treatment	**Number of cases (Total = 26)**	**Cases with available data (Total = 12)**	**Time to attain remission**			
			< 7days (Total = 0)	**7-14 days (Total = 10)**	**15 -40 days (Total = 1)**	**>40 days (Total = 1)**
2 weeks	1	1	-	1	-	-
4 weeks	19	7	-	6	-	1
5 weeks	1	1	-	-	1	-
6 weeks	1	1	-	1	-	-
8 weeks	4	2	-	2	-	-

Data is expressed as the total number of patients in their respective groups.

As shown in Table 3, the time to achieve remission was observed to be <7 days in 1 out of 13 (7.69%) cases, between 7-14 days in 6 out of 13 (46.15%) and 15-40 days in 4 out of 13 (30.76%) new-onset TTP cases.

Among the refractory TTP cases, 10 out of 12 (83.33%) attained normal platelet count within 7-14 days, 1 out of 12 (8.33%) cases within 15-40 days and 1 out of 12 (8.33%) cases took more than 40 days. The maximum percentage of remission in both new-onset and refractory TTP cases upon administration of Rituximab was observed to be between 7-14 days. Due to less sample size, it is difficult to comment on the duration of Rituximab treatment that caused earliest remission.

Table 4: Minimum duration of remission noted during follow-up in new-onset and refractory TTP cases after commencement of Rituximab treatment.

New-onset cases of TTP						
Duration of Rituximab treatment	**Number of cases (Total = 24)**	**Reports with available data (Total = 19)**	**Minimum duration of remission noted during follow-up**			
			1-10 m (Total = 5)	**11-20 m (Total = 6)**	**21-40 m (Total = 6)**	**>40 m (Total = 2)**
1 week	1	1	1	-	-	-
2 weeks	4	4	2	1	-	1
4 weeks	15	14	2	5	6	1
8 weeks	1	0	-	-	-	-
Refractory cases of TTP						
Duration of Rituximab treatment	**Number of cases (Total = 26)**	**Reports with available data (Total = 22)**	**Minimum duration of remission noted during follow-up**			
			1-10 m (Total = 5)	**11-20 m (Total = 10)**	**21-40 m (Total = 4)**	**>40 m (Total = 3)**
2 weeks	1	1	-	1	-	-
4 weeks	19	15	5	5	2	3
5 weeks	1	1	-	1	-	-
6 weeks	1	1	-	-	1	-
8 weeks	4	4	-	3	1	-

Data is expressed as the total number of patients in their respective groups; m, months.

Table 5: Number and sex of relapse and failure cases post-Rituximab therapy.

Duration of Rituximab therapy	**Number of Relapses/ Sex of the patient**		**Number of Failures/ Sex of the patient**	
	New-onset	**Refractory**	**New-onset**	**Refractory**
2 weeks	1 / F	-	-	-
4 weeks	-	2 / M;F	-	4 / F
6 weeks	-	1 / F	-	-
8 weeks	-	1 / F	-	-

M – Male, F - Female

Minimum duration of remission noted during follow-up in new-onset and refractory TTP cases upon commencement of Rituximab

As shown in Table 4, among the 19 new-onset TTP cases whose data was available out of the 24 cases, the period of remission lasted between 1-10 months in 5 (26.31%) cases, between 11-20 months in 6 (31.57%) cases, between 21-40 months in 6 (31.57%) cases and beyond 40 months in 1 (5.26%) case. The data of 22 patients among the 26 refractory TTP cases started on Rituximab was available. It was observed that the remission lasted for 1-10 months in 5 (22.72%) cases, 11-20 months in 10 (45.45%) cases, 21-40 months in 4 (18.18%) cases and more than 40 months in 3 (13.63%) cases. The sample size is insufficient to comment on the duration of Rituximab therapy that produced the longest period of remission.

Occurrence of relapses and failures in new-onset and refractory TTP cases post-Rituximab therapy

As shown in Table 5, 1 female patient out of 24 cases suffered a relapse after 2 weeks of Rituximab therapy. There was a 0% failure rate noted in the new-onset TTP cases post-Rituximab treatment. Among the 26 refractory TTP cases, 2 relapses were noted with the 4 week regimen, 1 male and 1 female. After completing the 6 week regimen, 1 female patient relapsed and yet another female patient relapsed after an 8 week regimen. Thus, among the refractory cases, a total of 3 female patients and 1 male patient relapsed after treatment with Rituximab. Among those who failed to respond to Rituximab even after 4 weeks of therapy, were 4 female patients. To sum up the observations, the number of relapses and failure rates were higher among the female population.

Obstacles in designing guidelines for TTP

TTP is a relatively uncommon but serious disease leading to neurological and cardiovascular complications that result in a mortality rate of >90% in untreated cases.[22] Hence, the sample size of these studies is often inadequate and long term follow-up of cases is difficult.

Patients with TTP and severe ADAMTS13 deficiency are heterogeneous, with remarkably variable presenting features.[23] 33% to greater than 90% of idiopathic TTP cases are related to a severe functional deficiency of ADAMTS13 in plasma. Its deficiency may be due either to mutations in the ADAMTS13 gene in the very rare inherited forms of TTP (Upshaw-Schulman syndrome) or to circulating auto-antibodies to ADAMTS13 in the more frequently acquired forms of TTP.[24] Patients can also have the characteristic presenting features and clinical course of TTP without severe ADAMTS13 deficiency or even with normal ADAMTS13 activity (> 50%),[23] and also patients can have severe ADAMTS deficiency for many years with no illness.[25]

Different researchers use different methods for estimation of ADAMTS13. Various assays use different substrates and denaturants, incubation times, detection methods and indication of vWF proteolysis.[26] This is a major factor that makes comparison between different treatment modalities difficult.

To worsen the situation further, a study by Weng & Levy, 2003,[27] demonstrated that polymorphisms in receptors for immunoglobulin G (FcγRs) affect the antibody-mediated cellular cytotoxicity of Rituximab in tumor cells. Patients with homozygous 158 valine/valine (V/V) alleles of FcγRIIIa showed a higher response rate to rituximab treatment. It is known that the FcγRIIIa of V allele has a higher affinity to human IgG1 than does the phenylalanine (F) allele and that cells bearing the FcγRIIIa V allele mediate ADCC more effectively.[28,29] Thus, polymorphisms are another important factor to be considered during the treatment of TTP.

Since, TTP is a serious condition; its treatment is usually multimodal as mentioned above. Numerous therapies or their combinations are started simultaneously. Since, patients respond differently to the treatments, it is difficult to interpret the extent of improvement caused by a single modality. There also might be dilution of effect of one treatment by others, for example, total plasma exchange therapy might wash out Rituximab from circulation before the latter can act leading to its failure. Hence, a common consensus needs to be reached among practitioners towards the optimal use of Rituximab along with other therapies for TTP.

CONCLUSION

Rituximab proved beneficial in terms of faster attainment and longer duration of remission, fewer relapses and failures, more so, in new-onset cases. Also, variability in assaying methods, FcγR polymorphisms, poor correlation between ADAMTS13 assays and clinical presentation of TTP, variable presenting features and interactions between treatments have been some of the vital drawbacks towards formulating guidelines for the treatment of TTP. Hence, large clinical studies are required to overcome the above mentioned differences in the therapy of TTP.

REFERENCES

1. Bukowski RM. Thrombotic thrombocytopenic purpura: a review. Prog Hemost Thromb. 1982;6:287–337.

2. Chemnitz J M, Hallek M and Scheid C. Long-term Efficacy of Rituximab Treatment in Thrombotic Thrombocytopenic Purpura. Eur Oncol Haematol. 2011;7(2):143–6.

3. Scully M, Hunt B J, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012 Aug;158(3):323-35. DOI: 10.1111/j.1365-2141.2012.09167.x

4. Iioka F, Shimomura D, Ishii T, et al. Short- and long-term effects of rituximab for the treatment of thrombotic thrombocytopenic purpura: four case reports. Int J Hematol.2012Aug 10. DOI 10.1007/s12185-012-1162-2

5. Bresin E, Gastoldi S, Daina E, et al. Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. Thromb Haemost. 2009;101:233–38.

6. Levine TD and Pestronk A. IgM antibody-related polyneuropathies: B-cell depletion chemotherapy using rituximab. Neurology.1999;52:1701–4.

7. Berentsen S, Tjonnfjord GE, Brudevold R, et al. Favourable response to therapy with the anti-CD20 monoclonal antibody rituximab in primary chronic cold agglutinin disease. Br J Haematol. 2001;115:79–83.

8. Specks U, Fervenza FC, McDonald TJ and Hogan MCE. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. Arthritis and Rheumatism. 2001;44:2836–2840.

9. Stasi R, Pagano A, Stipa E and Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood. 2001;98:952–957.

10. Dimopoulos MA, Zervas C, Zomas A, et al. Extended rituximab therapy for previously untreated patients with Waldenstrom's macroglobulinemia. Clin Lymphoma. 2002;3:163–166.

11. Mori A, Tamaru J, Sumi H and Kondo H. Beneficial effects of rituximab on primary cold agglutinin disease refractory to conventional therapy. Eur J Haematol. 2002;68:243–246.

12. Motto DG, Williams JA and Boxer LA. Rituximab for refractory childhood autoimmune haemolytic anemia. Isr Med Assoc J. 2002;4:1006–1008.

13. Perrotta S, Locatelli F, La Manna A, Cennamo L, De Stefano P and Nobili B. Anti-CD20 monoclonal antibody (rituximab) for life-threatening autoimmune haemolytic anaemia in a patient with systemic lupus erythematosus. Br J Haematol. 2002;116:465–467.

14. Remuzzi G, Chiurchiu C, Abbate M, Brusegan V, Bontempelli M and Ruggenenti P. Rituximab for idiopathic membranous nephropathy. Lancet. 2002;360:923–924.

15. Salopek TG, Logsetty S and Tredget EE. Anti-CD20 chimeric monoclonal antibody (rituximab) for the treatment of recalcitrant, life-threatening pemphigus vulgaris with implications in the pathogenesis of the disorder. J Am Acad Dermatol. 2002;47:785–788.

16. Zaja F, Iacona I, Masolini P, et al. B-cell depletion with rituximab as treatment for immune hemolytic anemia and chronic thrombocytopenia. Haematologica. 2002;87:189–195.

17. Zaja F, Vianelli N, Sperotto A, et al. B-cell compartment as the selective target for the treatment of immune thrombocytopenias. Haematologica. 2003a;88:538–546.

18. Zaja F, De Vita S, Mazzaro C, et al. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. Blood. 2003b;101:3827–3834.

19. Renaud S, Gregor M, Fuhr P, et al. Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. Muscle Nerve. 2003;27:611–615.

20. Trape G, Fianchi L, Lai M, et al. Rituximab chimeric anti-CD20 monoclonal antibody treatment for refractory hemolytic anemia in patients with lymphoproliferative disorders. Haematologica. 2003;88:223–225.

21. Zecca M, Nobili B, Ramenghi U, et al. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. Blood. 2003;101:3857–3861.

22. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. New England Journal of Medicine. 1991;325:393–397.

23. Furlan M, Robles R, Solenthaler M, Wassmer M, Sandoz P and Lämmle B. Deficient activity of von Willebrand factor-cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. Blood.1997;89:3097-3103.
24. Tsai HM and Shulman K. Rituximab induces remission of cerebral ischemia caused by thrombotic thrombocytopenic purpura. Eur J Haematol. 2003;70:183–185.
25. Moake JL, Turner NA, Stathopoulos NA, Nolasco LH and Hellums JD. Involvement of large plasma von Willebrand factor (vWF) multimers and unusually large vWF forms derived from endothelial cells in shear stress-induced platelet aggregation. J Clin Invest. 1986;78:1456-1461.
26. Sadler JE, Moake JL, Miyata T and George JN. Recent Advances in Thrombotic Thrombocytopenic Purpura. Hematology. 2004;407-423.
27. Weng W and Levy R. Two Immunoglobulin G Fragment C Receptor Polymorphisms Independently Predict Response to Rituximab in Patients with Follicular Lymphoma. J Clin Oncol 2003; 21:3940-3947.
28. Wu J, Edberg JC, Redecha PB, et al. A novel polymorphism of Fc-gamma-RIIIa (CD16) alters receptor function and predisposes to autoimmune disease. J Clin Invest. 1997;100:1059-1070.
29. Shields RL, Namenuk AK, Hong K, et al. High resolution mapping of the binding site on human IgG1 for Fc-gamma-RI, Fc-gamma-RII, Fcgamma-RIII, and FcRn and design of IgG1 variants with improved binding to the Fc-gamma-R. J Biol Chem. 2001;276:6591-6604.
30. Mak SK, Lo KY, Lo MW, et al. Refractory thrombotic thrombocytopenic purpura and membranoproliferative glomerulonephritis successfully treated with rituximab: a case associated with hepatitis C virus infection. Hong Kong Med J. 2009 Jun;15(3):201-8.
31. Koulova L, Alexandrescu D, Dutcher JP, O'Boyle KP, Eapen S and Wiernik PH. Rituximab for the Treatment of Refractory Idiopathic Thrombocytopenic Purpura (ITP) and Thrombotic Thrombocytopenic Purpura (TTP): Report of Three Cases. Am J Hematol. 2005;78:49–54. DOI: 10.1002/ajh.20243.
32. Kameda T, Dobashi H, Kittaka K, et al. Two cases of refractory thrombotic thrombocytopenic purpura associated with collagen vascular disease were significantly improved by rituximab treatment. Clin Rheumatol. 2007; 26:2159–2162. DOI 10.1007/s10067-007-0631-0.
33. Albaramki JH, Teo J and Alexander SI. Rituximab therapy in two children with autoimmune thrombotic thrombocytopenic purpura. Pediatr Nephrol. 2009; 24:1749–1752. DOI 10.1007/s00467-009-1186-x.
34. Scully M, Cohen H, Cavenagh J, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. Br J Haematol. 2007 Feb;136(3):451–61. DOI: 10.1111/j.1365-2141.2006.06448.x
35. Kuppachi S, Chander P and Yoo J. Membranous nephropathy and thrombotic thrombocytopenic purpura treated with rituximab. J Nephrol. 2009 Jul-Aug;22(4):561-564.
36. Magalini F, Stella A, Basaglia M, et al. Thrombotic thrombocytopenic purpura with severe neurological impairment: remission after Rituximab. Transfusion Medicine. 2011; 21(2): 140-143.
37. Ozdogu H, Boga C, Kizilkilic E, Yeral M, Kozanoglu I and Karatas M. A dramatic response to rituximab in a patient with resistant thrombotic thrombocytopenic purpura (TTP) who developed acute stroke. J Thromb Thrombolysis. 2007;23:147–150.
38. Millward PM, Bandarenko N, Chang PP, et al. Cardiogenic shock complicates successful treatment of refractory thrombotic thrombocytopenia purpura with rituximab. Transfusion. 2005 Sep;45(9):1481-1486.
39. Lombardi AM, Marinis GB, Scandellari R, et al. Clinical biological remission induced by rituximab in acute refractory chronic relapsing TTP. Thrombosis Research. 2010;126(2): e154-156.
40. Gutterman LA, Kloster B and Tsai HM. Rituximab Therapy for Refractory Thrombotic Thrombocytopenic Purpura. Blood Cells Mol Dis. 2002 May/Jun;28(3):385–391. DOI:10.1006/bcmd.2002.0522.
41. Yomtovian R, Niklinski W, Silver B, Sarode R and Tsai HM. Rituximab for chronic recurring thrombotic thrombocytopenic purpura: a case report and review of the literature. Br J Haematol. 2004 Mar;124(6):787–795.
42. Ojeda-Uribe M, Federici L, Wolf M, Coppo P and Veyradier A. Successful long-term rituximab maintenance for a relapsing patient with idiopathic thrombotic thrombocytopenic purpura. Transfusion. 2010 Mar;50(3):733-5. DOI: 10.1111/j.1537-2995.2009.02497.x.
43. Zheng X, Pallera AM, Goodnough LT, et al. Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and Rituximab. Ann Intern Med 2003;138:105–108.
44. Ahmad A, Aggarwal A, Sharma D, et al. Rituximab for Treatment of Refractory/Relapsing Thrombotic Thrombocytopenic Purpura (TTP). Am J Hematol. 2004;77:171–176.
45. Ling HT, Field JJ and Blinder MA. Sustained response with rituximab in patients with thrombotic thrombocytopenic purpura: A report of 13 cases and review of the literature. Am J Hematol. 2009; 84:418–421. DOI: 10.1002/ajh.21439.
46. Jayabose S, Dunbar J, Nowicki TS, Tugal O, Ozkaynak MF and Sandoval C. Rituximab therapy to prevent relapse in chronic relapsing thrombotic thrombocytopenic purpura (TTP) in a child. Pediatr Hematol Oncol. 2011 Mar;28(2):167-172. DOI: 10.3109/08880011003739414.
47. Kosugi S, Matsumoto M, Ohtani Y, et al. Rituximab provided long-term remission in a patient with refractory relapsing thrombotic thrombocytopenic purpura. Int J Hematol. 2005 Jun;81(5):433-436.
48. Reddy PS, Deauna-Limayo D, Cook JD, et al. Rituximab in the treatment of relapsed thrombotic thrombocytopenic purpura. Ann Hematol 2005;84:232–235.
49. Fakhouri F, Vernant JP, Veyradier A, et al. Efficiency of curative and prophylactic treatment with rituximab in ADAMTS13-deficient thrombotic thrombocytopenic purpura: a study of 11 cases. Blood. 2005;106:1932-1937.
50. Stein GY, Zeidman A, Fradin Z, et al. Treatment of resistant thrombotic thrombocytopenic purpura with rituximab and cyclophosphamide. Int J Hematol. 2004;80:94-96.
51. Patino W, Sarode R. Successful repeat therapy with rituximab for relapsed thrombotic thrombocytopenic purpura. J Clin Apher. 2007;22:17–20.

Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: S P Bhat, S Z Rahman. Rituximab Treatment in New and Refractory Thrombotic Thrombocytopenic Purpura (TTP) Patients: A Review. Int J Med Res Prof. 2016; 2(4):1-6.