Prophylactic treatment with bypassing agent FEIBA and Rituximab subsequent immune tolerance induction therapy to improve inhibitor eradication on resistant immune tolerance in severe hemophilia A patient with inhibitor

Shin-Nan Cheng, [1,2], Yeu-Chin Chen, [2,3]

[1]Department of Pediatric, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan, [2] Hemophilia Care & Research Center, Tri-Service General Hospital, Taipei, Taiwan, [3] Division Hematology/Oncology, Tri-Service General Hospital, Taipei, Taiwan

Introduction

The management of patients with severe hemophilia A and inhibitors unresponsive to standard immune tolerance is challenging. FEIBA prophylaxis among children with these condition resulted in significant reduction in annual joint bleed rate and inhibitor titer lower than at the start of prophylaxis. The use of rituximab combined with FVIII was responded some. In this paper, we present the effects of the use bypassing agent FEIBA prophylaxis then rituximab with concurrent FVIII treatment in 3 congenital hemophilia A with inhibitor resistant to ITI.

Materials and methods

Three patients with diagnosis of severe hemophilia A with inhibitor had received Hemate-P for ITI but failed with inhibitor titer around 8-20 BU/ml for 2-5 years. FEIBA prophylaxis was performed and inhibiter titer noticed down to below 10 BU/ml. Rituximab and concurrent rFVIII (100 U/kg/day) was treated until inhibitor disappearance and establishment of FVIII pharmacokinetics.

Results

The inhibitor titers were disappeared in all three patients and FVIII pharmacokinetics completely normalized in two cases within 1- 3 years. One patient had partial response with relapse at 3.6 years post-ITI with low responder inhibitors. This case received high dose rFVIII for prophylaxis therapy. The bleeding frequency seemed to be decreased or ceased following rituximab with rFVIII therapy.

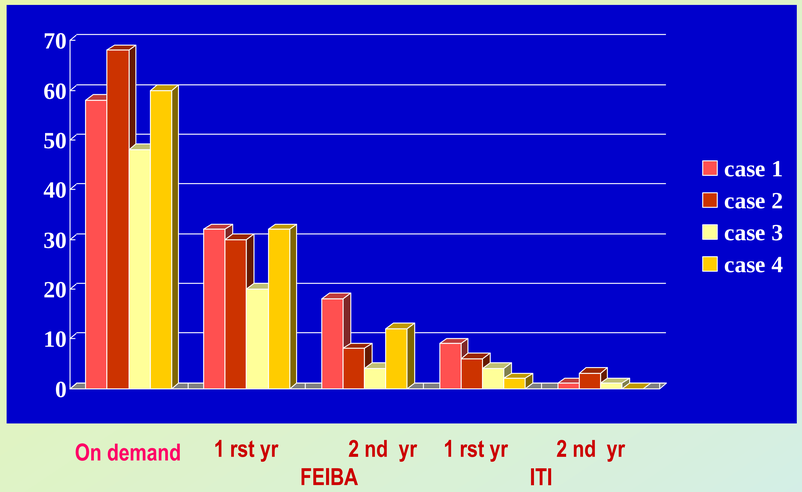
Case	#1	#2	#3
Age	17 yrs, M	20 yrs, M	15 yrs, M
Diagnosis	A, Severe	A, Severe	A, Severe
Age at HA diagnosis	1yr 3 month	4-momth	9-momth
FVIII gene defect	Intron 22 inversion	Intron 22 inversion	Exons 2-7 deletion
Treatment Modality	On prophylaxis	On demand	On prophylaxis
Age of anti-FVIII inhibiter onset	2 yrs	4 yrs	1.5 yrs old (Port-A infection)
Peak titer (BU/ml)	168	1600	70
1rst ITI (Hemate-P) Duration Inhibiter titer (BU)	 1.8 yrs 4.8-17.9 BU	 2 yrs 14-20 BU	 9 months 4.8-12.9 BU
Hemarthrosis treatment	rFVIIa / FEIBA	rFVIIa / FEIBA	rFVIIa / FEIBA
Bleeding (target joint)	Joint, muscle Elbow, right	Joint, muscle Ankle, bil	Joint, muscle soft tissue
FEIBA prophylaxis Regimen Duration Inhibiter level during FEIBA prophylaxis	 50-75U/Kg tiw 1 yrs 1.8-5.2	 50/Kg tiw 2.1 yrs 6.7-12.1	 50/Kg tiw 9 months 0.5-5.7
Initial inhibiter titer before 2nd ITI (BU/ml)	1.8	6.7	1.5
Rituximab with rFVIII Course Following period (yr)	375 mg/m^2 wk for 4 wks and 100 u/kg/day One 5.5	375 mg/m^2 wk for 4 wks and 100 u/kg/day one full course then one dose per 2-3 year 8.5	375 mg/m^2 wk for 4 wks and 100 u/kg/day one 6
Current inhibiter (BU/ml)	0	1.8- 6.1	0
Recovery time (%)	88	(10)	78
FVIII half time (hr)	9.2	(3.2)	7.8

Lymphocyte profile post-rituximab with rFVIII ITI therapy (patient # 2 and # 3)

months post-rituximab	6	7	9	11	12	15	17	25	30	-1
Anti-FVIII inhibitor titer (BU/ml)	5.7	774	378	100	3.3	1.6	0.9	1.3	6.1	8.3
CD3 (57-87)	78	94	96	96	95	79	82	74	70	80
CD19 (5-20)	0	0	0	0	1	17	15	25	26	17
CD8	39	48	48	46	44	37	38	34	37	43
CD4	37	43	46	50	47	40	42	34	32	37

months post-rituximab with rFVIII	3	5	8	11	14	-1
Anti-FVIII inhibitor titer (BU/ml)	0	0	0	0	0	0
CD3 (57-87)	68	74	76	82	88	62
CD19 (5-20)	0	0	2	8	10	20
CD8	37	48	48	48	43	42
CD4	38	48	49	50	47	31

Frequency of annual bleeding during post 1rst ITI, prophylaxis or rituximab with rFVIII (2nd ITI) therapy



Conclusion

Rituximab with concurrent administration of FVIII be useful in eradicating inhibitors in hemophilia A with inhibitors resistant to conventional ITI. The potential benefit of bypassing agent with rituximab is immense – both for patients who fail conventional ITI as well as upfront in most patients with high titer inhibitors to reduce the time required to achieve successful immune tolerance. Prospective randomized studies are required to determine the value of this agent in inhibitor management.