Ir Med J; September 2022; Vol 115; No. 8; P656

September 15th, 2022

Caplacizumab Use in a TTP Case Unresponsive to Conventional Therapy

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Abstract

Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is a rare but life-threatening disorder caused by severely reduced activity of ADAMTS13, causing platelet adhesion and formation of small-vessel platelet-rich thrombi, thrombocytopenia, and microangiopathic haemolytic anaemia.

Diagnosis

A 48-year-old female presented with acute generalized petechial rash, bruises, and fatigue. Bloods revealed thrombocytopenia, anaemia, 10% schistocytes. Her plasmic score was seven, and ADAMT13 was <5.

Treatment

Patient initially responded to plasma exchange and steroids, but thrombocytopenia recurred on day six of treatment, needing the addition of further immunosuppressive drugs and Caplacizumab.

Conclusion

TTP cases unresponsive to conventional regimens can represent a challenging situation; however, poor outcomes could potentially be avoided with a novel therapy like Caplacizumab. In our patient, this medication was well tolerated, and platelet count normalized after two days of its introduction.

Introduction

Acquired thrombotic thrombocytopenic purpura, is a life-threatening subtype of thrombotic microangiopathy (TMA) characterized by disseminated microvascular platelet-rich thrombi causing severe thrombocytopenia and microangiopathic haemolytic anaemia (MAHA).

This type of TTP is due to the presence of acquired autoantibodies against ADAMTS13, a specific von Willebrand factor (vWF) cleaving protease, causing severe deficiency of this plasma protein. Consequently, the ultra-large VWF multimers spontaneously bind to platelets resulting in VWF–platelet aggregates, leading to microthrombi formation, platelet consumption and MAHA[1].

TTP usually presents in adulthood, with the median age of onset being the fourth decade with a female predominance of 3:1[2]. Its hallmark is MAHA with thrombocytopenia and the presence of schistocytes in blood film[2].

Once suspected, early empirical treatment with therapeutic plasma exchange (PEX) is required, reducing mortality from 90% to 10-20%[1]. Measurement of ADAMTS13 activity is important for diagnosis, but this test has a prolonged turnaround time. Therefore, the PLASMIC score is utilized to stratify patients into low, intermediate, and high-risk categories, which directly correlates with the severity of ADAMTS13 deficiency[3].

As per ISTH guidelines, the first-line therapy for TTP is based on daily PEX and immunosuppressive therapy[4]. Caplacizumab was recently approved for treating TTP as adjunct therapy[5].

We present a case of TTP who responded initially to first-line therapy; however, platelet count dropped afterwards, and Caplacizumab was added.

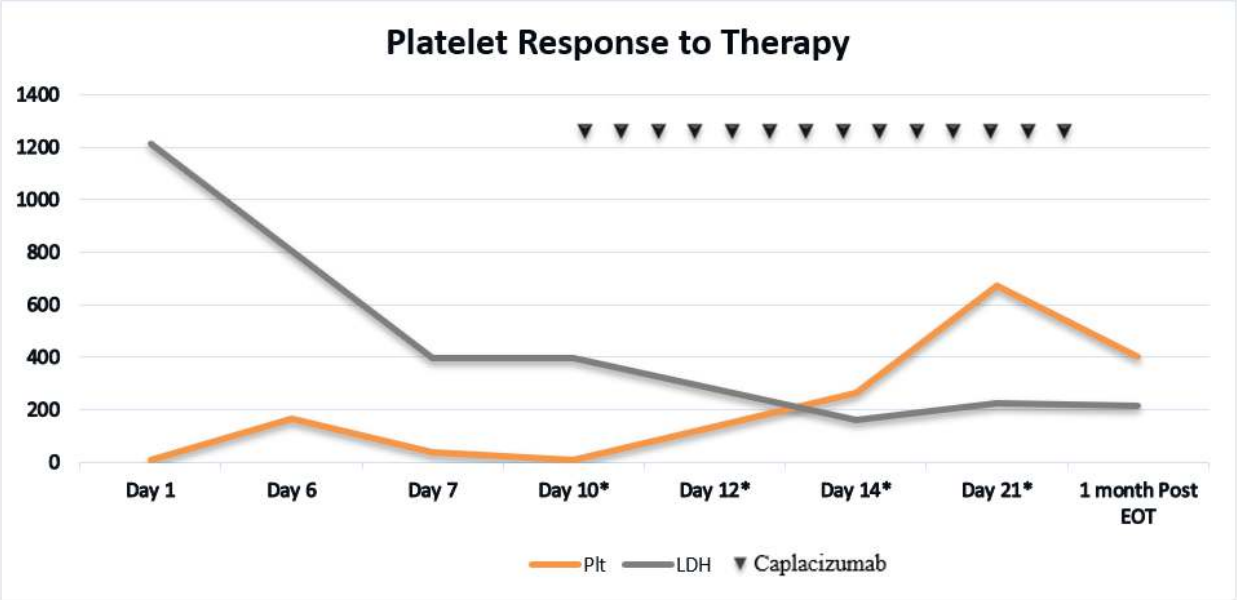
Case Report

A 48-year-old female with a past medical history of hypothyroidism presented to a regional hospital with three weeks of fatigue, occipital pressure like headache and progressive petechial rash and bruises on her limbs. Blood showed Hb 8.1 g/dl, Platelets $7x10^9$, reticulocytes $441x10^9$, 10% schistocytes in the blood film, hyperbilirubinemia 58umol/L, and negative coombs test. Her plasmic score was calculated to be seven, and consequently, she was transferred to a tertiary hospital, where PEX and a high dose of steroids were commenced immediately.

Test	Day 1	Day 6	Day 7	Day 10*	Day 12*	Day 14*	Day 21*	1 Month Post EOT	1 Year Post EOT
Hb	8.1	6.9	7.2	7.2	8	8.1	10.2	11.8	14.6
WC	8.9	11.1	10.9	19.6	13.6	10.9	10.9	6.97	6.8
Plt	**7**	**167**	**37**	**8**	**136**	**266**	**675**	**403**	**344**
Reticulocytes	441		414	337	354				
LDH	1213		398	398		163	227	215	194
T. Bilirubin	58	6	13	20	7	4	4	<3	8
Haptoglobin	<0.10		0.44						
Fibrinogen	2.6	1.9	1.9	2	2.1		2.4		
PT	11.4	11	10	11	10.4		10.3		
aPTT	23.4	23	21.5	19	23		21.5		
INR	1.1	1	1	1	1		1		
Urea	5.4	4.8	5.7	8.2	4.9	4.9	4.2	4.6	3.7
Creatinine	85	63	70	82	68	61	71	59	73
ALT	46	46	90	36	53	44	133	16	26
GGT	18	64	72	31	61	51	98	20	24
ADAMTS13	<5%						63%	92.2%	84.2%
DAT	-ve								
C3/C4	1/0.2								
B-HCG	-ve								
Viral screen	-ve								

Table 1: Laboratory results throughout the treatment period.

The following afternoon ADAMTS13 levels confirmed the diagnosis; therefore, daily PEX were continued along with steroids. Platelet count responded initially, reaching $167x10^9$ by day six of therapy. On day seven, the platelet count plunged to $37x10^9$, Rituximab was started, and a decision to add Caplacizumab was made, yet it was not readily available in the country until Day 10. Post 48hrs of administering Caplacizumab patient experienced a dramatic increase in platelet count, from 8 $x10^9$ to $136x10^9$. The patient was discharged on Day 21 with a platelet count of $675x10^9$ and continued daily Caplacizumab for a total of 30 days post-stopping PEX (Graph 1). On follow-up, she maintained a normal platelet count; her ADAMTS13 level was 92.2% a month after stopping Caplacizumab and 84.2% post one year. The patient had no complications during or post-treatment period with Caplacizumab.



Graph 1: Presenting Platelet and LDH response to therapy with arrow above showing introduction of Caplacizumab on day 10.

Discussion

TTP is a rare, serious disorder with an incidence of 4-11 per million in the USA, slightly less in the UK. Generally, females (especially of black ethnicity) are at higher risk, and the mortality rate can reach 90% if untreated (half of which occurs in the first 24 hours of presentation)[6].

Our case demonstrates a typical presentation of TTP. She initially responded to conventional therapy (PEX, Steroids and Rituximab); nevertheless, her platelet count dropped on day seven of therapy. PEX aims to replenish functional ADAMTS13 and eliminate vWF and its autoantibodies. Nevertheless, Glucocorticoids and Rituximab (Anti CD20 – found primarily on B cell surfaces) suppress anti-ADAMTS13 autoantibodies[7]. Generally, 15-32% of patients are refractory to PEX and Steroids[8], and in this setting, Caplacizumab is a novel option[9]. Caplacizumab targets the A1 domain of vWF, precluding its interaction with the platelet glycoprotein Ib-IX-V receptors and the subsequent thrombi formation[10]. Scully et al, showed on a double-blinded RCT on 145 TTP cases that the time for normalization of platelet count was shorter with the use of Caplacizumab, no patients developed refractory disease, and 31% had reduced hospitalization period[5].

Declaration of Conflicts of Interest:
None to declare.

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