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CASE REPORT

Prolonged Exposure to Caplacizumab as Rescue Therapy in Refractory Immune Thrombotic Thrombocytopenic Purpura

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Abstract: We describe a case of refractory thrombotic thrombocytopenic purpura (7 lines of therapy) in which caplacizumab was used over a 6-month period as rescue therapy. Caplacizumab maintained the patient in clinical remission until successful immunosuppression was achieved resulting in normal ADAMTS13 levels. This case illustrates the utility of caplacizumab therapy in treating refractory TTP.

Keywords: thrombotic thrombocytopenic purpura, caplac izumab, ADAMTS13, von Willebrand factor

Introduction

Caplacizumab is a humanized immunoglobulin fragment targeting the A1 domain (platelet binding site) of von Willebrand factor. The drug is recommended to be given as a daily subcutaneous injection to prevent platelet thrombosis and organ dysfunction associated with immune thrombotic thrombocytopenic purpura (TTP).[1,2] The International Society of Thrombosis and Haemostasis gives caplacizumab a "conditional recommendation" to treat TTP because clinical trial data with the drug did not clearly demonstrate a mortality advantage, and the high cost of the drug may be a barrier to its use.[3] Current prescribing information for caplacizumab recommends 30 days of treatment, with an additional 28 days suggested for persistent disease.

We describe a patient with immune TTP, refractory to 7 lines of therapy, who despite 6 months of severe ADAMTS13 deficiency (<5% of normal activity levels) achieved and maintained a stable normalized platelet count using outpatient caplacizumab until his ultimate response to bortezomib therapy.

Case Report

In 2004, a 47-year-old male with multiple auto-immune conditions (ulcerative colitis, Graves disease, diabetes) was diagnosed with immune TTP and treated with steroids, plasma exchange (PLEX), vincristine, splenectomy, and rituximab. He was in remission until 2019, at which point prednisone, rituximab, and PLEX led to a second remission lasting until 2021, when at age 63, he presented with recurrent TTP; ADAMTS13 activity was undetectable, and he had a positive ADAMTS13 inhibitor test at >8 Bethesda units. His clinical presentation was acute stroke, and there was exacerbation of his chronic kidney disease. During this time, he received prednisone (1 mg/kg daily), PLEX, (1 plasma volume daily for 8 days), and caplacizumab. Rituximab therapy was delayed so that the patient could receive and respond to COVID19 immunization. He was continued on caplacizumab because of persistently undetectable ADAMTS13 activity levels. During this time, ADAMTS13 inhibitor levels were consistently greater than 8 Bethesda units.

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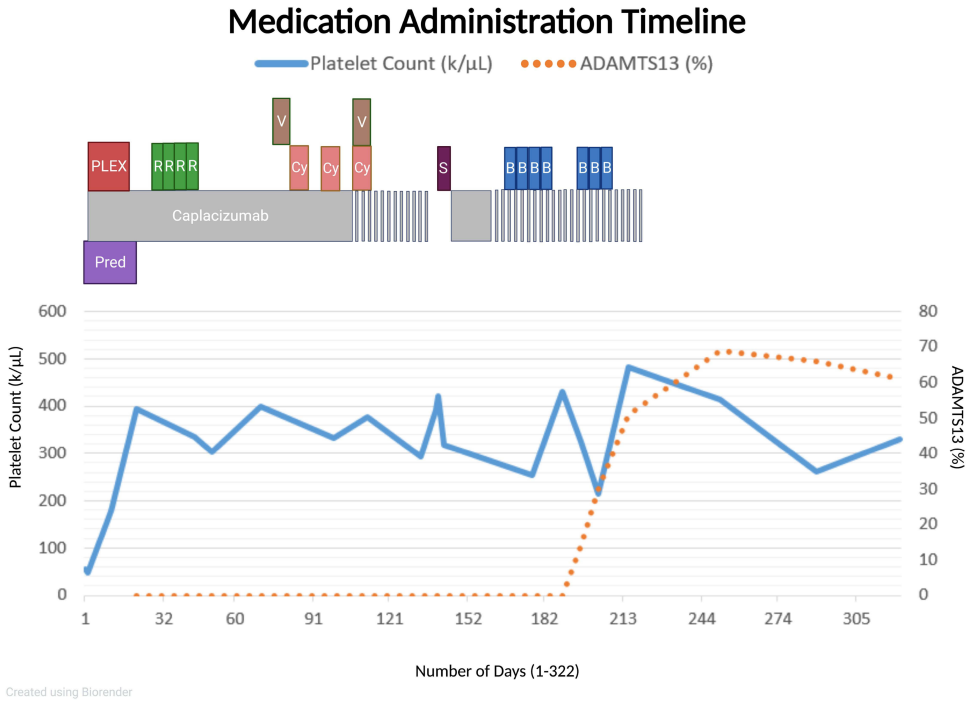

Figure 1 Medication timeline and response of platelet count and ADAMTS13 levels. The graph summarizes medications administered during the refractory TTP episode. Initial treatment was prednisone (day 1), PLEX and caplacizumab (day 2). Prednisone 1 mg/kg PO daily was continued d1-d10; PLEX daily d2-d9; and caplacizumab 11 mg SC daily d2-d115. By d20 the platelet count was 400,000/μL and the ADAMTS13 activity remained <5%. Rituximab 375 mg/m^2 IV weekly for 4 doses was given d28-d50. Vincristine 2 mg IV was given on d69 and d117. Cyclophosphamide was given 400 mg/m^2 IV every 3 weeks for 3 doses between d75-d117 before accessory spleen removal on d140. Caplacizumab was continued every other day from d117-d135 due to drug procurement issues. Daily caplacizumab was resumed post-splenectomy from d143-d162. Platelets remained stable during this time; however, ADAMTS13 activity remained undetectable. To conserve caplacizumab drug supply, alternate-day dosing was again used between d164-d210. Bortezomib 1.3 mg/m^2 SC was administered for refractory disease on d166, d169, d173, d177, d195, d198, and d202. ADAMTS13 activity increased after the fourth bortezomib dose. After stopping all medications, ADAMTS13 activity rose into the normal range.
Abbreviations: PLEX, plasma exchange; V, vincristine; Cy, cyclophosphamide; S, accessory spleen removal; B, bortezomib; R, rituximab.

Figure 1 summarizes the patient's treatments, platelet counts, and ADAMTS13 activity levels during this episode of TTP recurrence. Treatments included rituximab, vincristine, IV cyclophosphamide (400 mg/m^2 every 3 weeks for 3 doses),[4] accessory spleen removal, and bortezomib (1.3 mg/m^2 for 7 doses).[5] Steroids were not repeated due to poorly-controlled diabetes. Otherwise, treatment toxicity was minimal except for bortezomib-associated diarrhea and dehydration.

ADAMTS13 activity became detectable, and ADAMTS13 inhibitor began to decrease starting one month after bortezomib therapy was started. Caplacizumab was discontinued; he received ~6 months of caplacizumab therapy while awaiting response to immunosuppression. He did not experience significant bleeding events on caplacizumab. During the last 2 months of caplacizumab therapy, dosage was changed from daily to every other day (Figure 1). Platelet counts remained normal on the less-frequent dosing schedule. Laboratory monitoring of von Willebrand factor activity was not done during his treatment. At this time, the patient has been in complete remission for 7 months. Most recent ADAMTS13 activity was 80%.

Discussion

The patient ultimately achieved remission using bortezomib. A recent review identified 32 patients reported in the literature and at a single institution who received bortezomib therapy for refractory TTP.[6] ~70% of patients had a complete response; median time to relapse was 7 months, and 6% of patients had adverse events.[6]

Caplacizumab induces acquired von Willebrand disease, and consequently, a potential bleeding risk in TTP patients. A recent literature review of the drug's safety profile raised concerns about major bleeding to argue against routine use of caplacizumab to treat immune TTP.[7] Our patient received ~ 6 months of daily or alternate-day caplacizumab and

experienced no major bleeding events. Future clinical trials should address this issue and determine whether caplacizumab's efficacy benefits outweigh its bleeding risks.

Recent data from a European registry of TTP cases treated with or without caplacizumab indicate that all treatment-related outcomes, including mortality were improved with caplacizumab therapy.[8] The above case report suggests that it is feasible to use caplacizumab as rescue therapy for refractory TTP patients. Caplacizumab drug costs can be reduced by utilizing an alternate-day dosing regimen.[9]

Ethical Statement

This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from the patient in this study for publication of this case report. Institutional approval was not required for this case report.

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Disclosure

GMR is a consultant for and reports personal fees from Sanofi. MB declares that she has no conflicts of interest in this work. MF declares that she has no conflicts of interest in this work. JAG declares that he has no conflicts of interest in this work.

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