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Caplacizumab

Updated: June 7, 2021.

OVERVIEW

Introduction

Caplacizumab is a humanized single variable domain immunoglobulin (nanobody) against the von Willebrand factor, which is used to treat acquired thrombotic thrombocytopenic purpura. Caplacizumab increases the risk of minor and major bleeding episodes and is associated with a low rate of serum aminotransferase elevations during therapy, but has not been linked to instances of clinically apparent liver injury.

Background

Caplacizumab (cap" la siz' ue mab) is a humanized single variable domain of immunoglobulin (nanobody) directed against the von Willebrand factor which has been developed as therapy of acquired thrombotic thrombocytopenic purpura (TTP). Acquired TTP is a rare but severe and often fatal syndrome marked by appearance of thrombocytopenia, hemolytic anemia, and multiple microvascular thromboses, with kidney, heart and renal dysfunction due to the development of autoantibodies against ADAMTS13, a vWF cleaving metalloprotease that controls platelet aggregation by vWF. The deficiency in ADAMTS13 results in formation of large platelet-vWF aggregates that cause the pathologic thromboses. Therapy of aTTP generally involves emergency plasma exchange transfusions to reduce levels of the pathogenic autoantibody as well as immunosuppression (usually high doses of corticosteroids or rituximab) to decrease the autoantibody production. Caplacizumab binds to activated vWF and decreases thrombus formation allowing for increases in plasma ADAMTS13 activity. In several small randomized controlled trials, caplacizumab therapy was associated with elevations in serum ADAMTS13, a shorter time to clinical response (rise in platelet counts) and fewer complications, exacerbations and relapses of TTP. Caplacizumab was approved in the United States for use in combination with plasma exchange therapy in patients with acquired TTP in 2019. The recombinant "nanobody" is available in vials of 11 mg per mL under the brand name Cablivi. Administration of caplacizumab is timed with the plasma exchange procedures, generally given initially as an intravenous infusion of 11 mg before the first plasma exchange, followed by 11 mg subcutaneously at the conclusion of each plasma exchange; after the plasma exchange period, 11 mg subcutaneously once daily for 30 days. Common side effects include local infusion reactions, headaches and fatigue, but most characteristically bleeding episodes, typically epistaxis, bruising and gingival and rectal bleeding. Severe adverse events include serious bleeding episodes such as subarachnoid and intracerebral hemorrhage which can be fatal. Early recognition and prompt management of these side effects is an integral component of proper use of caplacizumab.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations arise in 1% to 2% of treated patients, but are generally asymptomatic and transient and rarely necessitate discontinuation of caplacizumab injections. Serum ALT elevations above 5 times the upper limit of normal (ULN) occurred in less than 1% of patients in registration trials of caplacizumab but there were no instances of clinically apparent liver injury. Since approval and more general use of caplacizumab, there have been no reports of clinically significant liver injury attributed to its use.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

The possible mechanisms of liver injury due to caplacizumab are unclear unless they might be caused by excessive bleeding. Monoclonal antibodies and immunoglobulins are generally taken up by cells and metabolized to short peptides and amino acids.

Drug Class: Monoclonal Antibodies, Hematologic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Caplacizumab – Cablivi®

DRUG CLASS

Hematologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Caplacizumab	915810-67-2	Single Variable Domain Immunoglobulin	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 07 June 2021

Abbreviations used: TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor.

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway-targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL, Hilal-Danan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1203-36.

(Textbook of pharmacology and therapeutics).

Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knöbl P, Wu H, et al. TITAN Investigators. Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2016;374:511–22. PubMed PMID: 26863353.

(Among 75 patients with acquired TTP treated with caplacizumab or placebo, the time to response was shorter with the caplacizumab and exacerbations were fewer while the bleeding episodes were more frequent [54% vs 38%], while other adverse events were uncommon and mild, ALT elevations arose in 2 [6%] on caplacizumab and none on placebo).

Duggan S. Caplacizumab: first global approval. Drugs. 2018;78:1639–42. PubMed PMID: 30298461.

(Review of the structure, mechanism of action, clinical efficacy and safety of caplacizumab shortly after its approval by the European Medicines Administration as therapy of acquired TTP).

Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. HERCULES Investigators. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019;380:335–46. PubMed PMID: 30625070.

(Among 145 patients with acquired TTP treated with caplacizumab or placebo during plasma exchange and for 30 days afterwards, time to platelet normalization, duration of hospitalization, plasma exchange sessions, thrombotic events, and recurrences were less with caplacizumab, while mucocutaneous bleeding episodes were more frequent [65% vs 48%]; no mention of ALT elevations or hepatotoxicity).

Kaczmarek V, Holle J, Astudillo R, Kempf C, Bufler P, Müller D. Caplacizumab for relapsing thrombotic thrombocytopenic purpura. Pediatr Nephrol. 2019;34:1625–8. PubMed PMID: 31177334.

(10 year old girl with recurrent acquired TTP was treated with caplacizumab in addition to plasma exchange during the second episode and, unlike with the first, had a rapid and complete response within 3 days that was sustained without evidence of adverse events).

Chander DP, Loch MM, Cataland SR, George JN. Caplacizumab therapy without plasma exchange for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019;381:92–4. PubMed PMID: 31269374.

(63 year old woman and Jehovah's Witness developed acquired TTP but refused blood transfusions, and was eventually treated with caplacizumab without plasma exchange and had a rapid and complete clinical response with only a single and minor bleeding episode).

Knoebl P, Cataland S, Peyvandi F, Coppo P, Scully M, Kremer Hovinga JA, et al. Efficacy and safety of open-label caplacizumab in patients with exacerbations of acquired thrombotic thrombocytopenic purpura in the HERCULES study. J Thromb Haemost. 2020;18:479–84. PubMed PMID: 31691462.

(Among 28 patients who had an exacerbation of disease during a placebo controlled trial of caplacizumab therapy of acquired TTP [Scully 2019], who then received open label therapy with the active drug, responses were prompt and only one patient had a relapse after stopping therapy; adverse events included catheter site hemorrhage, headache and epistaxis but there was no mention of ALT elevations or hepatotoxicity).

Völker LA, Kaufeld J, Miesbach W, Brähler S, Reinhardt M, Kühne L, Mühlfeld A, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv. 2020;4:3085–92. PubMed PMID: 32634236.

(Retrospective data analysis from 60 patients with acquired TTP treated with caplacizumab in 29 medical centers in Germany found that therapy led to rapid response and normal platelet levels within a median of 3 days, only one death [1.4%] and with few serious adverse events [vaginal bleeding in one patient] and no mention of ALT elevations or hepatotoxicity; in 6 instances patients were treated successfully with caplacizumab alone, without exchange transfusions).

Sukumar S, Lämmle B, Cataland SR. Thrombotic thrombocytopenic purpura: pathophysiology, diagnosis, and management. J Clin Med. 2021;10:536. PubMed PMID: 33540569.

(Review of the history of discovery, clinical characterization and elucidation of pathogenesis of acquired and congenital TTP, and description of actions of vWF and ADAMTS13 in coagulation and thrombosis and

abnormalities that characterize aTTP with review of current and future directions in its management including use of caplacizumab).