COMMENTARY

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TO THE EDITOR:

Caplacizumab as frontline therapy in addition to standard treatment in iTTP

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We read with interest the meta-analysis performed by Djulbegovic et al about the use of caplacizumab as a treatment for patients with immune thrombotic thrombocytopenic purpura (iTTP).[1] We respectfully disagree with some of the conclusions drawn by the authors.

Firstly, the authors state that the addition of caplacizumab to the standard of care did not significantly reduce all-cause mortality compared with standard of care alone. All-cause mortality was not a primary endpoint in any of the studies included in their meta-analysis, and no trial using caplacizumab was designed or powered to demonstrate a significant reduction in all-cause mortality.[2-6] It is wellknown that iTTP is a life-threatening condition. Without treatment, mortality was high (>90% in the 1920s), and treatment with steroids with or without plasma (plasma infusion in the 1970s and plasma exchange more recently) reduced mortality to 10% or 20%.[7] However, mortality remains a concern. Table 1 shows mortality reported in several TTP registries across the United States and Europe, ranging from 7% to 25% with a mean of 11.7%.[8-14] According to these data, a randomized controlled trial (RCT) with 955 patients would have an 80% power to detect a 50% reduction in mortality (from 10% to 5%) with caplacizumab comparable with placebo at a 5% significance level and a 10% dropout rate.

Secondly, the authors also state that frontline caplacizumab may not benefit all patients with iTTP. Currently, as stated before and shown in Table 1, the mortality of patients with an acute episode of iTTP is as high as 25%, death occurs primarily during the early days after diagnosis, and some of the patients could not even receive any treatment.[12,13] This fact highlights the importance of an early diagnosis and the rapid use of drugs that interfere with uncontrolled formation of microvascular thrombi. Although we have a better understanding of the pathophysiology of iTTP, treatment with plasma exchange and immunosuppression is not addressed to microvascular thrombosis. The current treatment replenishes the functional ADAMTS13 enzyme and controls the underlying autoimmune disease. The addition of caplacizumab at the very beginning will block the adhesion of platelets to the very high molecular weight von Willebrand factor (VWF) multimers, thus preventing the formation of the intravascular platelet thrombi responsible for the clinical manifestations of the disease from the first day of the treatment.[15] Therefore, we strongly believe that caplacizumab must be started as frontline therapy in addition to standard treatment along with plasma exchange and immunosuppression. We developed a therapeutic protocol at our hospital (CASPERI)[16] in accordance with this previous explanation as well as in line with recommendations given in international and national evidence-based guidelines[17,18] and real-world data.[4-6,19]

Finally, the authors emphasize that the addition of caplacizumab was associated with an increased risk of bleeding. In fact, the meta-analysis found that caplacizumab increased the risk of any bleeding but caused no major bleeding or intracranial hemorrhage (ICH). Caplacizumab interferes with VWF, a key protein in hemostasis. Accordingly, von Willebrand disease–like bleeding is expected, and mucocutaneous bleeding has been reported in preclinical trials and RCTs.[2,3] More recently, patients with acute episodes of iTTP experiencing ICH while receiving caplacizumab have been reported.[20,21] Therefore,

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Table 1. Mortality in TTP registries

First author[ref]	Publication year	Registry	Period	Patients	Mortality n(%)	Time to death (days)*
Coppo[8]	2010	France	2000-2007	160	18 (11)	NR
Page[9]	2017	Oklahoma	1995-2015	78	10 (13)	NR
Alwan[10]	2017	United Kingdom	2009-2016	292	32 (11)	4 (1-39)
Colling[11]	2020	Boston	2004-2017	109	8 (7)	6.5 (0-27)
Pascual-Izquierdo[12]	2021	Spain	2015-2017	203	15 (7)	NR (6 of them before starting treatment)
Del Rio[13]	2022	Spain	2004-2018	102	8 (8)	9.5 (0-36)
Adeyemi[14]	2022	United States	2015-2019	666	167 (25)	33 (13-178)

NR, not reported.
*Time to death in days is reported as median (range).

postmarketing surveillance is important in this setting to refine, confirm, or deny the safety of caplacizumab for the general population.

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