

TO THE EDITOR:

More on the use of frontline caplacizumab in immune-mediated thrombotic thrombocytopenic purpura

Adrien Picod,^{1,2} Ygal Benhamou,^{1,3} Raïda Bouzid,¹ Agnès Veyradier,^{1,4,5} and Paul Coppo^{1,6,7}

¹Centre National de Référence des MicroAngiopathies Thrombotiques, AP-HP, Paris, France; ²Service de réanimation médico-chirurgicale, Hôpital Avicenne Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, France; ³Service de Médecine Interne, CHU Charles Nicolle and Normandie Univ, UNIROUEN, F 76031 Rouen, France; ⁴Laboratoire ADAMTS13, Hôpital Lariboisière, AP-HP.Nord, Université de Paris, Paris, France; ⁵Institut de recherche Saint Louis, Université de Paris, Paris, France; ⁶Service d'Hématologie, AP-HP, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, Sorbonne-Université (AP-HP.6), Paris, France; and ⁷Centre de Recherche des Cordeliers, Paris, France

We read with interest the work by Djulbelgovic et al, recently published in *Blood Advances*.¹ In this meta-analysis of randomized controlled trials (RCTs) and observational “real-life” studies of immune-mediated thrombotic thrombocytopenic purpura (iTTP) treatment, the authors reach the conclusion that “frontline addition of caplacizumab does not significantly reduce all-cause mortality compared with standard of care alone, although it reduces the risk of refractory disease, shortens time-to-response, and improves exacerbation rates, at the expense of increased relapse and bleeding risk.” Consequently, Djulbelgovic et al question the International Society on Thrombosis and Haemostasis (ISTH) recommendations to use frontline caplacizumab in iTTP, given that it does not reduce the risk of death or relapse.²

We disagree with these statements that do not match our experience and our understanding of the current literature. We believe that the methodology used by the authors provided misleading conclusions that are not supported by most recent works. It is important to note that the first real-world experience studies have been conducted during a learning period, when modalities of treatment were still highly variable. In the last few years, accumulated experiences with a more consensual and homogenized use of caplacizumab have allowed for the specification of 2 key modalities in the use of this agent: timing of initiation and treatment duration.

In the precaplacizumab era, the mortality rate of iTTP episodes still reached 12% and most iTTP-related deaths occurred during the first 10 days, often in the context of a refractory disease.³⁻⁵ Thus, the benefit of caplacizumab, which undeniably shortens time to recovery and decreases the risk of refractoriness, lies in the initial phase and not as a step-up therapy. It should be remembered that only such frontline strategy has been tested in RCTs.

Even before the use of caplacizumab in the standard of care, deaths during an acute iTTP episode were rare events, thus making the study of mortality as an outcome difficult. In consequence, it is necessary to consider many homogeneously managed patients to demonstrate a statistically significant modification of the risk of death. Overcoming this methodological limitation frequently requires the use of composite outcomes as highlighted by the authors. Another solution is to restrict the analysis to the time frame for which the treatment is supposed to provide the best effect. Thus, in the initial phase, the integrated analysis of the TITAN and HERCULES trials has indeed found a significant mortality reduction with the use of caplacizumab compared to standard of care alone.⁶

Performing a meta-analysis of real-world studies considering a population treated heterogeneously and reflecting the progressive improvements and adjustments in the use of a new therapeutic agent cannot lead to definitive conclusions. Importantly, “frontline” caplacizumab refers to caplacizumab as part of the initial treatment of an acute iTTP episode, ie, at the same time or within the very first days after the first

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For data sharing, contact the corresponding author, Paul Coppo (paul.coppo@aphp.fr).

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therapeutic plasma exchange (TPE).^{2,7} It has indeed been repeatedly shown that patients receiving caplacizumab in a delayed manner had worse outcomes.⁸⁻¹⁰ Of note, in the UK study included in the meta-analysis, caplacizumab initiation was delayed >48 hours after TPE initiation for 5 out of 6 deceased patients (up to 21 days).⁹ In contrast, in our experience of frontline caplacizumab where patients who received caplacizumab beyond day-5 after TPE were considered not to have been treated optimally and therefore excluded, outcomes including survival are much more favorable.¹¹ Because the higher death rate in caplacizumab-treated patients of the UK study has a major impact on the results of the meta-analysis, the overall conclusion that frontline caplacizumab is not associated with a reduction of the mortality risk does not appear robust.

In the analysis of Djulbegovic et al, the conclusion that caplacizumab increases the risk of relapse, ie, a recurrence of iTTP manifestations occurring beyond day 30 after TPE (considered a new distinct episode, whereas a recurrence before day 30 is termed exacerbation and considered a continuation of the prior episode), largely reflects the results of early RCTs. Caplacizumab only prevents the formation of new microthrombi by inhibiting the interaction between von Willebrand factor and platelets but has no action on the formation of anti-ADAMTS13 antibodies, a mechanism that needs to be addressed by concomitant immunosuppression. Therefore, it is not surprising that the risk of iTTP recurrence is high if caplacizumab is stopped too early, ie, while ADAMTS13 activity is still depressed due to the delayed action of the immunosuppressive regimen. In the phase 2 TITAN trial, after a 28-days post-TPE treatment, patients in the caplacizumab arm experienced significantly more relapses than the placebo arm. It should be noted that in most cases ($n = 7/11$), these were early relapses, occurring within 10 days of caplacizumab cessation in patients with a persistent severe ADAMTS13 deficiency.¹² Of note, patients in the caplacizumab arm received rituximab less frequently. In consequence, treatment in the phase 3 trial HERCULES could be extended for a maximum of 28 days beyond the initial 30 days after TPE along with adjustment of immunosuppression if severe ADAMTS13 deficiency persisted. Nevertheless, despite this recommendation, all 6 patients in the caplacizumab arm who experienced a relapse did so because the treatment was interrupted while ADAMTS13 activity was still undetectable.⁷ From these observations, it becomes clear that caplacizumab does not increase relapses; instead, the 28-day treatment after TPE with caplacizumab brings patients beyond the exacerbation period, into the period corresponding to the definition of relapse and during which relapses are observed because caplacizumab is interrupted before ADAMTS13 reaches a protective level.¹³

The time to achieve ADAMTS13 activity $\geq 20\%$, a threshold empirically considered to be protective, is highly variable. In our experience of patients treated with an optimal immunosuppressive regimen including the systematic use of frontline rituximab, ADAMTS13 $\geq 20\%$ is achieved after a median of 28 days after TPE but 10% of patients still have a depressed ADAMTS13 activity after 56 days, emphasizing the need to tailor the duration of therapy to the monitoring of ADAMTS13 activity. Such strategy is currently under evaluation (NCT04720261).

To date, we have treated 215 iTTP patients with our standard regimen, including frontline caplacizumab (within 4 days of TPE initiation).¹¹ Death and refractoriness occurred in 2 cases (1%) each, including 1 iTTP-related death. Twelve patients (5.6%) experienced an exacerbation mostly related to an interruption of caplacizumab while ADAMTS13 was still depressed ($n = 5/12$); in the remaining cases, exacerbation occurred typically in a context of infection ($n = 4/12$). Time to clinical response with daily TPE was 4 days (interquartile range [IQR], 4-6). Nine patients (4.2%) relapsed after a median follow-up of 7 months (IQR, 1.25-20). In 3 cases, relapse resulted again from an interruption of caplacizumab in a context of persistent severe ADAMTS13 deficiency (manuscript in preparation). Taken together, these results extend our previous work, and strengthen the view that frontline caplacizumab, in association with TPE and immunosuppression improves iTTP outcomes.

Hence, we do not believe that the analysis of Djulbegovic et al reflects the best practice in the use of frontline caplacizumab as suggested by the ISTH guidelines and other experts' recommendations,^{2,14} but rather gives a glimpse of the hazard associated with a step-up/salvage strategy of initiation, and/or a premature interruption of caplacizumab.² Contemporary knowledge of the disease and of the pharmacology of caplacizumab should allow a precise monitoring and tailored therapy to avoid these pitfalls.

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ORCID profiles: A.P., 0000-0002-0639-5598; R.B., 0000-0003-1419-3758; P.C., 0000-0002-4618-2095.

Correspondence: Paul Coppo, Centre National de Référence des Microangiopathies thrombotiques, Service d'hématologie, Hôpital Saint-Antoine, AP-HP; 184 Rue du Faubourg Saint-Antoine, 75012 Paris, France; email: paul.coppo@aphp.fr.

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