CORRESPONDENCE

Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

TO THE EDITOR: Scully et al. (Jan. 24 issue)[1] reported that in the HERCULES trial (A Phase III Double-Blind, Randomized, Parallel Group, Multicenter Placebo-Controlled Trial to Study the Efficacy and Safety of Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura), caplacizumab accelerated the normalization of platelet counts in patients with acquired thrombotic thrombocytopenic purpura. The survival curves in Figure 1 of their article are initially close, diverge and reconverge multiple times, and finally cross at approximately day 17. The estimated hazard ratio of 1.55 indicates that the time to platelet normalization was shorter with caplacizumab; this conclusion, however, depends on the proportional-hazards assumption, and it cannot hold if the survival curves cross. Unlike risk, hazard is not a probability measure, and thus the hazard ratio cannot be interpreted to show that patients receiving caplacizumab are 1.55 times as likely as patients receiving placebo to have platelet normalization. Using reconstructed individual-level data,[2] we found no evidence that the medians or quartiles of the distributions were significantly different (Table 1). In a model-free approach to quantifying the treatment effect,[3-5] the difference between the 20-day restricted mean survival times was 1.33 days (95% confidence interval [CI], −0.31 to 2.97), a result that favors caplacizumab but is not significant. Unlike the hazard ratio, the difference in restricted mean survival times does not require assumptions such as proportional hazards.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The authors of the HERCULES trial suggest that persistent ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity of less than 10% could justify continuation of caplacizumab treatment beyond the studied 30-day trial period. Although levels of less than 10% are clearly associated with recurrence,[1] we argue that the appro-

Table 1. Percentiles of Time to Confirmed Normalization of Platelet Count and Restricted Mean Survival Time Based on the Reconstructed Data.*

Measure	Caplacizumab	Placebo	Difference (95% CI)	P Value
		days		
Time to confirmed normalization of platelet count (95% CI)†				
25th percentile	1.84 (1.73 to 1.96)	1.99 (1.77 to 2.71)	0.15 (−0.12 to 0.91)	0.69
50th percentile	2.76 (2.45 to 2.88)	2.89 (2.78 to 3.79)	0.13 (−0.06 to 0.97)	0.67
75th percentile	2.99 (2.91 to 4.06)	4.51 (3.79 to 9.89)	1.52 (−0.03 to 5.09)	0.48
Restricted mean survival time (95% CI)‡	3.51 (2.44 to 4.58)	4.84 (3.60 to 6.09)	1.33 (−0.31 to 2.97)	0.11

* The data on time to confirmed normalization of the platelet count were extracted and reconstructed[2] from Figure 1 of the original article with the use of the "digitize" package in R software, version 3.5.1 (R Project for Statistical Computing). CI denotes confidence interval.
† The 25th, 50th, and 75th percentiles of survival time were estimated with the R software "survival" package.
‡ The restricted mean survival times were estimated by calculating the area under the Kaplan–Meier curve with the R software "survRM2" package.

priate treatment of such patients remains unclear. Resolution of thrombocytopenia is a standard end point for plasma exchange in patients who are not receiving caplacizumab, but it may misrepresent the degree of recovery of ADAMTS13 activity and thereby falsely reassure medical providers who administer the drug. Caplacizumab reduces platelet consumption by preventing platelet adherence to von Willebrand factor multimers, but it does not itself appear to affect ADAMTS13 or autoantibody levels and may lead to premature cessation of plasma exchange while high antibody titers linger, as suggested by the higher number of patients with relapse in the caplacizumab group than in the placebo group (6 patients vs. 0 patients). It is unclear whether ongoing caplacizumab treatment, earlier modifications in immune suppression, or further plasma exchange in these scenarios would be more beneficial. We suggest that additional studies, perhaps including alternative surrogates for determining the end of plasma exchange and immune suppression modification, such as ADAMTS13 levels, are warranted.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS AND A COLLEAGUE REPLY: In response to Yang et al.: the Kaplan–Meier curves cross at the tail, at approximately day 17, when there is one patient left in each trial group and the survival probability is less than 5%. In this type of scenario, the Cox proportional-hazards analysis is still valid. The evaluation of the proportional-hazards assumption based only on visual assessment of the Kaplan–Meier curves is, however, misleading. As was prespecified in the statistical analysis plan, the adequacy of the Cox proportional-hazards model was tested graphically (by the empirical score process) and numerically (by supremum testing). Both analyses showed that the proportional-hazards assumption was met. Thus, the hazard ratio can be used to assess the treatment effect of caplacizumab.

The restricted mean survival time analysis in the letter was performed with the use of reconstructed data, which might not be accurate. Using the real data, we performed the same analysis. The difference between the 20-day restricted mean survival times was 1.45 days (95% CI, 0.05 to 2.87), which favors caplacizumab and is significant (P=0.04).

In response to Olson and Samuelson-Bannow: in the TITAN trial,[1] early relapses after treatment cessation occurred in 22% of the patients in the caplacizumab group, all of whom had persistent low ADAMTS13 activity by the time treatment was stopped, 30 days after cessation of plasma exchange. In the HERCULES trial, caplacizumab treatment could be extended beyond 30 days after the period of daily plasma exchange in cases of unresolved immunologic disease (e.g., low ADAMTS13 activity), for a maximum duration of 28 days together with the administration of immunosuppressive therapy that was adjusted as needed. This led to fewer patients in the caplacizumab group having early relapse in the HERCULES trial (six patients [8%]) than in the TITAN trial, and all the patients with early relapse in the HERCULES trial still had persistently low ADAMTS13 activity at the time of treatment cessation. The trial provides evidence that caplacizumab prevents relapse when treatment is extended until complete resolution of the underlying immunologic disease.

The results from the HERCULES trial confirmed that caplacizumab leads to a faster platelet count normalization and prevention of exacerbations, consequently reducing the need for unnecessary intensive therapies, such as plasma exchange. The normalization of ADAMTS13 activity can be achieved with adequate immunosuppression administered while the patients continue to receive caplacizumab therapy.

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Ms. Minkue Mi Edou reports being employed by Ablynx, a Sanofi company. Since publication of their article, Drs. Scully and Callewaert report no further potential conflict of interest.

1. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med 2016;374:511-22.

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