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THROMBOSIS AND HEMOSTASIS

Comment on Coppo et al, page 733

TTP: the evolution of clinical practice

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In this issue of *Blood*, Coppo et al[1] have documented that caplacizumab is an effective targeted immunotherapy for thrombotic thrombocytopenic purpura (TTP) that has the potential to change established clinical practice.

Without appropriate treatment, only 10% of patients with acquired, autoimmune TTP survive (see table). In the 1970s, the first effective treatments were reported. A turning point for clinical practice was a publication in 1991 of the Canadian randomized clinical trial that documented the effectiveness of plasma exchange (PEX).[2] TTP was transformed into a treatable disorder, with 78% survival. PEX is only a temporizing treatment; it removes anti-ADAMTS13 autoantibodies and replaces ADAMTS13. Immunosuppression is also required. PEX, together with corticosteroids and rituximab, remains the standard treatment of TTP in 2020.

Caplacizumab was approved for treatment of TTP in 2018 (Europe) and 2019 (United States). Clinical trials documented that its addition to the standard therapy caused more rapid platelet recovery with fewer days of PEX and then fewer exacerbations when PEX was stopped.[3] Caplacizumab is a nanobody that binds to the A1 domain of von Willebrand factor (VWF), blocking platelet adhesion. Its effectiveness suggests that platelet binding to the ultralarge multimers of VWF that occur in TTP contributes to the characteristic microvascular thromboses. Blockade of platelet binding to VWF can cause minor bleeding; severe bleeding rarely occurs.[3] Caplacizumab is also only a temporizing treatment; immunosuppression is also required. Recent guidelines for treatment of TTP published by the International Society of Thrombosis and Haemostasis suggest that caplacizumab be added to the traditional regimen for initial treatment: PEX, corticosteroids, and rituximab.[4]

Evolution of TTP treatment

The past (1924 to 1975): *No effective treatment* 10% survival
The beginning (1976 to 1990): *Effective treatment* Whole-blood exchange transfusion (1976) Plasma infusion (1977)
The present (1991 to 2020): *Increasingly effective treatment* Plasma exchange (1991, 78% survival) Corticosteroids (1991) Plasma exchange, corticosteroids, rituximab (2002) Plasma exchange, corticosteroids, rituximab, caplacizumab (2020, 99% survival)*
The future? (2021-): *Simpler, safer treatment* Caplacizumab, rituximab

*Coppo et al.

The transition from clinical trials to clinical practice is not simple. Uniformity of patients and their management is the goal of clinical trials. Clinical practice is different. Patients are inevitably more diverse; the experience of treating physicians is also more diverse. The gap between clinical trials and clinical practice is illustrated by the experience with caplacizumab. Because current treatment of TTP is effective and familiar, caplacizumab has not been widely accepted as initial treatment. The report by Coppo et al in this issue of *Blood* provides a bridge from the clinical trials to clinical practice.

Coppo's study was possible because of their established organization of clinical practice sites throughout France. This organization adopted a common protocol for the use of caplacizumab. Thirty-two sites enrolled 90 patients (median, 2 patients per site). Caplacizumab was used as initial treatment together with PEX, corticosteroids, and rituximab. Only 1 patient, an 83-year-old woman, died; the cause was pulmonary embolism. Only 1 patient did not double her platelet count within 4 days. These outcomes were a significant improvement compared with 180 patients treated by these hematologists during the previous years.

A concurrent report of an observational study involving 29 sites throughout Germany was even more closely related to the "real world" of clinical practice.[5] Sixty patients were treated with caplacizumab, in addition to PEX, corticosteroids, and (in 48 patients) rituximab; only 1 death was reported. The outcomes of these 2 studies are consistent with our understanding that caplacizumab promptly blocks microvascular thrombosis. Prompt blockade of microvascular thrombosis may also limit ischemic organ injury that could diminish adverse long-term outcomes, such as cognitive impairment and

depression.[6] The data from these 2 reports suggest that caplacizumab should be considered for initial treatment of TTP.

Why not consider caplacizumab for initial treatment of patients with TTP? A principal reason is cost. A single treatment (10 mg) costs $8000.[7] The anticipated regimen of caplacizumab is daily treatment until ADAMTS13 recovery is established by immunosuppression, which may require 30 days ($240 000). Are the benefits of caplacizumab worth this cost? A recent analysis of adding caplacizumab to standard care concluded that it is not cost-effective.[7] I accept this conclusion for caplacizumab added to standard care. Standard care is to continue PEX until the platelet count is normal for 2 days and then to resume PEX if the platelet count subsequently decreases, described as exacerbation. However, what if standard care was changed? If a patient is treated with caplacizumab, it would be reasonable to stop PEX as soon as the platelet count begins to recover, because recovery will continue. Exacerbation will not occur while caplacizumab is continued. After the initial IV administration of caplacizumab, subsequent daily doses are given subcutaneously, making home treatment possible and shortening hospitalization.

A discussion of standard care leads to a seismic consideration. Is PEX, our standard of care for 29 years, still necessary? Could caplacizumab replace PEX, exchanging 1 temporizing treatment for another? Treatment without PEX may be simpler and safer. PEX requires insertion of a central venous catheter and mobilization of skilled personnel with their apheresis equipment. Complications of PEX are common, often related to the central venous catheter; they can be serious, even fatal.[8]

What would treatment without PEX look like? Last year, we had an experience with a familiar patient who had had multiple previous relapses of TTP. She had an early relapse with only mild symptoms and moderate thrombocytopenia. She knows her disease. She asked not to be hospitalized, not to have PEX, and not to have corticosteroids. We agreed. Her regimen was caplacizumab and rituximab. Her symptoms promptly resolved, and her platelet count promptly recovered.[9] Others have had similar experiences using caplacizumab without PEX.[5,10]

Coppo et al have provided a giant step from the clinical trials of caplacizumab to clinical practice. This step allows us to look into the future. It makes us reconsider the management of TTP for the first time in 29 years.

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REFERENCES

1. Coppo P, Bubenheim M, Azoulay E, et al. A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. *Blood*. 2021;137(6):733-742.
2. Rock GA, Shumak KH, Buskard NA, et al; Canadian Apheresis Study Group. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *N Engl J Med*. 1991;325(6):393-397.
3. Scully M, Cataland SR, Peyvandi F, et al; HERCULES Investigators. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019; 380(4):335-346.
4. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18(10):2496-2502.
5. Völker LA, Kaufeld J, Miesbach W, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. *Blood Adv*. 2020;4(13): 3085-3092.
6. George JN. TTP: long-term outcomes following recovery. *Hematology Am Soc Hematol Educ Program*. 2018;2018:548-552.
7. Goshua G, Sinha P, Hendrickson JE, et al. Cost effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura [abstract]. *Blood*. 2020;136(suppl 1):18-19. Abstract 901.
8. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv*. 2017; 1(10):590-600.
9. Sukumar S, George JN, Cataland SR. Shared decision making, thrombotic thrombocytopenic purpura, and caplacizumab. *Am J Hematol*. 2020;95(4):E76-E77.
10. Völker LA, Brinkkoetter PT, Knöbl PN, et al. Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab. *J Thromb Haemost*. 2020;18(11): 3061-3066.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Uy et al, page 751

DARTs point the way forward in AML

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In this issue of *Blood*, Uy et al report the results of a multicenter phase 1/2 study of a CD3ε × CD123 bispecific drug in patients with relapsed/refractory acute myeloid leukemia (AML).[1] The drug, flotetuzumab, belongs to a class of dual affinity retargeting proteins (DARTs) that bring together effector cells (for example, T cells) with target cells (for example, CD123-expressing AML blasts). The concept is similar to that of blinatumomab, a CD3ε × CD19 bispecific T-cell engager now in routine clinical use in B-cell acute lymphoid leukemia. The target molecule, CD123, is not unique to AML blasts and is also expressed on some normal hematopoietic cell populations.[2] Nonetheless, CD123 is among the leading potential cell surface targets for immunotherapy in AML with 24 active studies listed on www.clinicaltrials.gov (accessed 7 September 2020).

The dose-finding cohort of the trial enrolled 42 patients and led to a "recommended phase 2 dose" of 500 ng/kg per day by continuous infusion after a stepwise dose escalation. Forty-six patients were then enrolled to the dose expansion cohort. Almost all patients treated at the recommended phase 2 dose experienced infusion-related reactions/cytokine release syndrome, although these were generally mild and easily managed with dose interruptions and/or tocilizumab. Neurologic