

Caplacizumab for Acute Thrombotic Thrombocytopenic Purpura

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Acute thrombotic thrombocytopenic purpura (aTTP) is a rare microangiopathic hemolytic anemia. Standard of care currently includes plasma exchange and immunosuppressive agents, including glucocorticoids, vincristine, and rituximab. Even with these therapies, relapse occurs in 36% of patients, and mortality ranges from 10% to 20%. Caplacizumab is a novel agent approved for the treatment of adult patients with aTTP in conjunction with plasma exchange and immunosuppressive therapies. It works by binding to the A1 domain of von Willebrand factor (VWF), blocking platelets from binding to VWF and aggregating. In clinical trials, patients who received caplacizumab compared with placebo were more likely to have a normalization of their platelet count, a lower rate of recurrence, and a lower incidence of the composite of aTTP-related death, recurrence, or major thromboembolic event. The side effect profile is rather benign and includes epistaxis, headache, and gingival bleeding. Caplacizumab is only available through specialty pharmacy services due to its high cost. Providers should be aware of and prepared for the prior authorization process required to assist their patients in gaining access to the medication. Currently, there is no formal consensus regarding caplacizumab's place in therapy for patients with aTTP, but it remains an option for refractory cases.

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare form of microangiopathic hemolytic anemia affecting 1 to 13 per million people every year (Stanley & Michalski, 2019). In clinical practice, a triad of thrombocytopenia, schistocytosis, and elevated lactate dehydrogenase is suggestive of aTTP (Moake, 2002; Sivilotti, 2019). Long-term comorbidities include cognitive deficits, depression, arte-

rial hypertension, and premature death (Deford et al., 2013). Even with treatment, relapse occurs in 36% of patients, and mortality ranges from 10% to 20% (Stanley & Michalski, 2019).

An episode of aTTP is the result of a breakdown in the body's normal platelet adhesion response (Sivilotti, 2019). Inhibitory autoantibodies impair the activity of ADAMTS13, a circulating zinc metalloprotease that can cleave von Willebrand fac-

tor (VWF). This leads to an excess buildup of ultra-large VWF multimers, platelet adhesion and clumping, microthrombi made up of VWF and platelets, and ischemic organ damage (Lämmle, 2016; Scully et al., 2019; Sivilotti, 2019).

Plasmapheresis is the gold standard of treatment for aTTP, as it removes both large multimers of VWF and the autoantibodies against ADAMTS13, and afterward, the infusion of fresh frozen plasma replenishes ADAMTS13 (Sivilotti, 2019). When plasma exchange alone does not resolve an episode of aTTP (platelet count recovery to $\geq 150,000 \text{ mm}^3$), additional therapies can be initiated; glucocorticoids decrease autoantibody overproduction, vincristine depolymerizes platelet microtubules, and rituximab depletes peripheral CD20 memory B lymphocytes.

MECHANISM OF ACTION

Caplacizumab (Cabliivi) is a novel agent approved by the U.S. Food & Drug Administration in February 2019 with an indication for adult patients with aTTP in combination with plasma exchange and immunosuppressive therapy (Sanofi, 2019a). It represents a new class of therapeutic agents, nanobodies, which operate similarly to naturally occurring, heavy chain-only antibodies (Sanofi, 2019a). It works by binding to the A1 domain of VWF, blocking platelets from binding to VWF and aggregating (Sanofi, 2018). Caplacizumab is 90% bioavailable, and the elimination half-life is concentration and target-level dependent. Unbound drug is thought to be renally cleared, and there are no dose adjustment recommendations for either hepatic or renal impairment.

CLINICAL TRIALS

Caplacizumab was first studied in a phase II, single-blind, parallel-design, randomized, placebo-controlled study (TITAN; Peyvandi et al., 2016). The trial enrolled 75 patients 1:1 to receive either caplacizumab or placebo along with the standard of care (daily plasmapheresis and immunosuppressive therapy). Those in the caplacizumab arm received an IV loading dose of 10 mg 6 hours to 15 minutes prior to the first plasma exchange followed by a subcutaneous injection of 10 mg within 30 minutes of completion of each plasma exchange. Patients continued to receive 10-mg

subcutaneous injections of caplacizumab for 30 days after the final day of plasma exchange for up to 90 days.

The primary outcome of this study was the time to confirmed normalization of the platelet count ($\geq 150,000 \text{ mm}^3$), which was reduced by 39% (event rate ratio, 2.2; 95% confidence interval [CI] = 1.28–3.78; $p = .005$) in the caplacizumab group compared with placebo (3.0 days vs. 4.6 days; Peyvandi et al., 2016). Additionally, complete remission (defined as confirmed normalization of the platelet count and no exacerbations) was seen more often in the caplacizumab group than in the placebo group (81% vs. 46%). Patients who received caplacizumab had fewer exacerbations compared with placebo (3 vs. 11), but more patients in the caplacizumab group experienced a relapse of TTP (defined as new thrombocytopenia occurring more than 30 days after the end of daily plasma exchanges) within the 1-year follow-up period compared with the placebo group (31% vs. 8%).

After TITAN came a phase III, double-blind, randomized, parallel group, multicenter placebo-controlled trial (HERCULES; Scully, 2019). HERCULES enrolled 145 patients and randomized them 1:1 to receive either caplacizumab or placebo. Caplacizumab in this trial was dosed in the same way as TITAN with the addition that caplacizumab could be extended for a maximum of 28 days beyond the 30 days post-plasma exchange period if risk factors for recurrence, such as persistent low ADAMTS13 levels, remained.

The primary outcome was the time from the first IV administration of caplacizumab or placebo to normalization of the platelet count ($\geq 150,000 \text{ mm}^3$), with discontinuation of daily plasma exchange within 5 days (Scully, 2019). Patients who received caplacizumab were 1.55 times more likely to have a normalization of the platelet count as patients who received placebo (1.55; 95% CI = 1.09–2.19; $p = .01$). The composite of TTP-related death, recurrence of TTP, or a major thromboembolic event showed 74% lower incidence with caplacizumab than with placebo ($p < .001$). Time to normalization of organ-damage markers (including lactate dehydrogenase, cardiac troponin I, and serum creatinine) occurred somewhat sooner in the caplacizumab group than in the placebo group. Refractory TTP was seen in 0 patients in

the caplacizumab group and 3 patients in the placebo group ($p = .06$).

Finally, recurrence of TTP was 67% lower with caplacizumab than with placebo ($p < .001$; Scully, 2019). In a post-hoc analysis of the HERCULES trial, 26 patients in the placebo group and 2 patients in the caplacizumab group who experienced an exacerbation agreed to trial open-label caplacizumab. In this subset of patients, the median time to platelet response was 3.49 days, and only one patient experienced further thromboembolic events, leading the authors to conclude that caplacizumab is well tolerated in exacerbations as well (Knoebl et al., 2019).

ADVERSE EVENTS

The most common treatment-emergent adverse events reported from both trials included epistaxis (29%), headache (21%), and gingival bleeding (16%; Sanofi, 2018). Monitoring parameters for adverse effects include ADAMTS13 levels and platelet trends via complete blood counts. Symptomatic patients should also be monitored for end-organ damage (electrocardiogram, troponins, etc.) and neurologic changes (brain MRI). If a patient is on an anticoagulant, it does not need to be discontinued, but the patient should be closely monitored. Caplacizumab should be discontinued if a patient experiences a severe bleeding episode, and if necessary, VWF/factor VIII concentrate can be given to correct homeostasis.

Of note, while both trials used a 10-mg dose of caplacizumab, a dose recovery study performed

after HERCULES showed that the mean dose that can be withdrawn from a vial of caplacizumab is 11 mg (Sanofi, 2018). As a result, the data based on the 10-mg dosing is actually reflective of an 11-mg dose, and caplacizumab should be administered according to the instructions in the package insert, which mirror the schedule outlined in HERCULES (Table 1).

COST AND LOGISTICS

Although TITAN and HERCULES accomplished the goal of proving the safety and efficacy of caplacizumab, questions still remain regarding drug affordability, acquisition, and administration logistics. The average wholesale price per Cablivi injection kit (i.e., per syringe) is \$8,760 (Hanlon & Metjian, 2020; Lexicomp, 2019), and the estimated average cost of treating a typical aTTP episode is \$270,000 (Sanofi, 2019a). Whether a patient is started on caplacizumab inpatient for emergent care of an aTTP episode or outpatient for a refractory case, Sanofi provides a “Hospital Guide for Cablivi” that assists providers with transitions of care (Sanofi, 2019b). The manufacturer provides several services, including financial support based on eligibility, benefits verification via Biologics (a specialty pharmacy provider for Cablivi), and supplemental training for self-administration after hospital discharge via clinical educators.

If a provider intends for the patient to continue caplacizumab upon discharge or after beginning the medication in an outpatient infusion center, a prior authorization (PA) should be initiated

Table 1. Dosing Strategy for Caplacizumab

	Treatment period	Caplacizumab administration ^a
Standard treatment	Day 1	Caplacizumab 11 mg IV 6 hours to 15 minutes prior to PLEX, then caplacizumab 11 mg subcutaneous 30 minutes after PLEX
	Day 2 through end of daily PLEX treatment	Caplacizumab 11 mg subcutaneous daily 30 minutes after PLEX
	After completion of PLEX treatment	Caplacizumab 11 mg subcutaneous daily for 30 days
Extension of therapy	Additional treatment if risk factors for recurrence or signs of persistent underlying disease ^b	Caplacizumab 11 mg subcutaneous daily for up to 28 days

Note. PLEX = plasma exchange.

^aAdministered in addition to the patient's current immunosuppressive therapy.

^bExample includes persistent, severe ADAMTS13 deficiency.

as soon as possible. For hospital systems that do not have an associated outpatient pharmacy that can dispense the medication, the “Cablivi Patient Solutions Enrollment Form” can be filled out and faxed to Biologics (Sanofi, 2019c). Along with pertinent labs, PAs should include providers’ progress notes outlining the patient’s case and rationale for starting caplacizumab. Ideally, documentation would encompass diagnosis, history of present illness, previous therapies trialed, treatment failures, and future therapeutic plans.

Another component for health systems to take into consideration is how patients will receive plasma exchange in conjunction with caplacizumab doses. Whether it is best and most cost effective for the patient to receive plasma exchange during an extended inpatient stay or in an outpatient infusion center seems to be at the discretion of the individual health system. Some case reports also suggest that caplacizumab may still be effective even if it is given without the use of plasma exchange (Chander et al., 2019). However, this is not how the drug was studied, and more data are necessary to validate administration in this way.

IMPLICATIONS FOR ADVANCED PRACTITIONERS

Caplacizumab’s place in treatment guidelines is still being defined. An expert statement on the ICU management of patients with aTTP recommends caplacizumab in addition to plasma exchange, corticosteroids, and rituximab as first-line therapy in critically ill patients with severe aTTP (Azoulay et al., 2020). Whether early caplacizumab and rituximab should be used routinely irrespective of aTTP severity is still unclear.

The authors of the expert statement also make note that after pooling the results of both TITAN and HERCULES, caplacizumab was associated with a significant reduction in health-care resources, including ICU and hospital length of stay, number of plasma exchange sessions, and volume of plasma required to achieve remission. Some note that hospitals might be hesitant to incorporate caplacizumab into formularies out of concerns for overtreatment of less severe patients and inflating health-care costs (Hanlon & Metjian, 2020). A recent cost-effectiveness analysis showed that over a 5-year period, the projected incremental cost-

effectiveness ratio was \$1,482,260, which is well over the accepted 2019 US willingness-to-pay threshold of \$195,300 (Goshua et al., 2021). Cost aside, caplacizumab will likely provide a benefit for refractory cases, including patients who have failed trials of plasma exchange and immunosuppressive agents, as can already be seen in limited case reports (Cilla et al., 2020; Kaczmarek et al., 2019).

CONCLUSION

After considering the evidence, it can be concluded that caplacizumab is a safe and efficacious treatment for aTTP. Current practice offers few treatment options to aTTP patients, and despite best management efforts, recurrence rates remain high. There is a clear benefit to using caplacizumab in aTTP to normalize thrombocytopenia, and side effects can be monitored and managed. While case managers, nurse supervisors, and social workers will play an integral role in the transitions of care surrounding this medication, physicians and advanced practitioners, including pharmacists, should also be aware of the assistance programs available to patients and the most efficient ways to help patients gain access to the therapy. ●

Disclosure

The authors have no conflicts of interest to disclose.

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