The Long and Winding Road for New Treatments for Acquired Thrombotic Thrombocytopenic Purpura

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Acquired thrombotic thrombocytopenic purpura (TTP) is caused by autoantibodies against ADAMTS13, resulting in severe deficiency of plasma ADAMTS13 activity. For decades, standard treatment of TTP has consisted of plasma exchange and corticosteroids. New treatment modalities are emerging in an attempt to minimize organ damage in the acute setting. Although the mechanistic insights into the pathogenesis of acquired TTP have improved over the last 10 years, only 1 new drug has made it into clinical practice for acquired TTP. A recent publication in ATVB on loading platelets with rADAMTS13 (4) for the treatment of acquired TTP and the recent market access of caplacizumab has led to this short update on emerging therapies for acquired TTP.

Blocking the GPIb/vWF (von Willebrand Factor) Interaction

Anifabtide

The platelet GPIb antagonist anifabtide has been investigated in a murine model of TTP in 2016. It was shown that anifabtide could dramatically inhibit the adhesion and aggregation of murine and human platelets on a collagen surface under arterial shear stress, in the presence or absence of plasma ADAMTS13 activity.1 Intraperitoneal administration of anifabtide mitigated spontaneous thrombocytopenia and prevented shigatoxin-induced TTP in Adamts13−/− and disease-susceptible mice. There are currently no clinical trials in patients with acquired TTP.

Anti-VWF Aptamer ARC1779

ARC1779 specifically binds to the A1 domain of vWF. Although ARC1779 treatment significantly inhibited vWF activity and vWF-dependent platelet activation and raised platelet counts in patients with acquired TTP,2 phase II and III trials have been terminated due to slow inclusion rates.

Caplacizumab

The TITAN and HERCULES trials have shown the efficacy of caplacizumab in the treatment of acute TTP.3 Caplacizumab is a nano-antibody directed against the A1 domain of vWF. Not only was the time to reach a platelet count response shortened, caplacizumab also resulted in a significant reduction in the incidence of the composite endpoint of acquired TTP-related death, recurrence of acquired TTP or major thromboembolic event during the study treatment period compared with placebo (incidence rate 12.7% vs 49.3%). A significant reduction in the incidence of acquired TTP recurrence was seen with caplacizumab at a dose of 10mg during the overall study period (12.7% vs 38.4%, corresponding to a 67% reduction; P < 0.001).3 Caplacizumab (Cablivi) has just been granted marketing authorization from the European Commission (Fig. 1).

Recombinant ADAMTS13

rADAMTS13 (BAX 930)

Until now, only patients with the congenital form of TTP have been treated with rADAMTS13. Currently, there are no trials in patients with acquired TTP.
Platelet Loading With rADAMTS13

Recently, researchers developed a novel approach by delivering rADAMTS13 (recombinant ADAMTS13) using platelets as vehicles. The endocytosed rADAMTS13 within platelets remains intact and active and is stored in α-granules. The rADAMTS13 in platelets is released and effectively inhibits platelet adhesion and aggregation under arterial shear stress in a perfusion model as well as in plasma from a patient with acquired TTP. Furthermore, transfusion of rADAMTS13-loaded platelets into Adamts13−/− mice dramatically reduces the rate of thrombus formation in the mesenteric arterioles after FeCl3 injury.

Ultimately, treatment of acquired TTP will be a blend of tapering the antibody response, supplementing the deficient ADAMTS13 and inhibiting the GPIb/vWF interaction. It will still be a long road before the optimal regimen has been found.

References

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