Von Willebrand Factor — A New Target for TTP Treatment?

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Thrombotic thrombocytopenic purpura (TTP), a rare thrombotic microangiopathy, is defined by a mechanical hemolytic anemia, severe thrombocytopenia, and visceral ischemia due to systemic platelet-rich microthrombi. Specifically in TTP microthrombi, von Willebrand factor, not fibrinogen, is the protein that binds to platelets. Von Willebrand factor is a multimeric glycoprotein that is crucial for physiologic platelet adhesion and aggregation at high shear rates of blood flow, and the largest von Willebrand factor multimers are the most adhesive. The hemostatic power of von Willebrand factor is regulated by a specific cleaving metalloprotease named ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 repeats, member 13). Since 1998, the link between TTP, von Willebrand factor, and ADAMTS13 has been elucidated: a severe functional deficiency of ADAMTS13 (due mainly to anti-ADAMTS13 autoantibodies and very rarely to ADAMTS13 gene mutations) causes the accumulation of platelet-hyperadhesive, ultralarge von Willebrand factor multimers in the blood, spontaneously inducing the formation of microthrombi in the microvasculature.

The discovery of ADAMTS13 led to both the solution to the enigma of the pathophysiology of TTP and the understanding of the basis for the efficacy of daily plasma exchange, which has been used empirically since the 1990s. Before plasma exchange, TTP was often fatal. It is now clear that therapeutic plasma is a source of ADAMTS13 that acts as replacement therapy and that the exchange process removes the anti-ADAMTS13 autoantibodies (Fig. 1).

Today, plasma exchange remains the frontline therapy in patients with TTP. A possible alternative replacement therapy for the future is recombinant ADAMTS13, which has not yet been tested in humans. In addition, to target anti-ADAMTS13 autoantibodies, several approaches to immune-complex inhibition have been used: glucocorticoids (frontline therapy with plasma exchange), vincristine and cyclophosphamide (rarely used), splenectomy (salvage therapy), and for about the past 10 years, rituximab (a monoclonal antibody targeting the CD20 antigen of B lymphocytes) (Fig. 1). The efficacy of these immunomodulating treatments has not been proved by means of randomized, prospective trials, but several case series have shown that rituximab is very promising in the treatment of refractory TTP or a relapse of TTP. Other immunologic approaches with the use of cyclosporine (an inhibitor of T-cell activation), eculizumab (an anti-C5 monoclonal antibody), or bortezomib (a proteasome inhibitor) were also used anecdotally to treat TTP (Fig. 1).

Despite these major therapeutic advances, the global mortality associated with TTP is about 15%. In the patients who die, the vicious cycle of von Willebrand factor–dependent thrombi formation is most likely not disrupted fast enough by therapies targeting ADAMTS13 and its specific autoantibodies. Thus, a more direct and rapidly acting treatment approach would be to inhibit the binding of von Willebrand factor to platelets, either by reducing the size of von Willebrand factor multimers with N-acetylcysteine or, more powerfully, by blocking the binding of von Willebrand factor to platelets.

Caplacizumab is a single-variable-domain immunoglobulin (Nanobody) directed to the A1 region of von Willebrand factor, which specifically inhibits its interaction with platelet glyco-
protein Ib under high shear conditions. Caplacizumab showed its safety and efficacy in preventing thrombosis in a baboon model of acquired TTP. In this issue of the Journal, Peyvandi et al. present the TITAN study, an international, multicenter, phase 2, randomized, placebo-controlled study of caplacizumab that was designed to assess its efficacy and safety (as an adjunct to plasma exchange) in patients with acquired TTP. Seventy-five patients were enrolled. As compared with placebo, caplacizumab showed a short-term efficacy by reducing both the time to platelet count normalization and the early exacerbation rate, but it did not have an effect on the risk of relapse of TTP. Caplacizumab was associated with an increased tendency toward bleeding as compared with placebo, a potential outcome of blocking the interaction of von Willebrand factor with platelets.

It is interesting to speculate that effective TTP treatment will involve a combination of interventions that target different aspects of the pathophysiology. ADAMTS13 replacement with either normal plasma or perhaps recombinant product would restore processing of von Willebrand factor multimers to the appropriate size. Formation of new microthrombi can be blocked by interfering with the binding of von Willebrand factor to platelets, as shown by the efficacy of caplacizumab. The autoantibody to ADAMTS13 can be inhibited by selective suppression of the B cells that produce the antibody — for example, with rituximab or other anti–B-cell antibodies. A remaining goal is the disaggregation of platelet-rich thrombi. Many questions remain with regard to the optimal timing and sequencing of these therapeutic options in the management of TTP, not only in the curative treatment of patients in acute phases but also in the prevention of relapses.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Achilles’ Lead: Will Pacemakers Break Free?

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Pacemaker leads, which connect the chest-wall generator of a pacemaker to the pacing electrode in the heart, are the “Achilles’ heel” of pacing and defibrillation systems. Over time, they wear out, which often necessitates their risky removal and replacement. In addition, transvenous leads provide a portal into the vascular space, which increases the risk of infection. Patients with traditional pacemakers and defibrillators are also susceptible to hematomas and pocket infections in the chest wall where the generators lie. Thus, a self-contained leadless pacemaker that can be placed directly into the heart is an appealing prospect.

Reports of two recent nonrandomized, industry-sponsored studies of leadless pacemakers have now been published in the Journal. In the first study, published in September, the Nanostim device (St. Jude Medical) was evaluated; now, Reynolds et al. report on the second study, in which the Micra device (Medtronic) was examined. Although the devices were not directly compared in these two studies, they appear to be remarkably similar (Table 1). The volume of each device is approximately 1 cm³. Each attaches to the right ventricle — the Nanostim with a helical wire screw, the Micra with tines. Both systems are delivered to the right ventricle through the femoral vein and contain a reattachable mechanism for removal. Both devices pace only the ventricle and thus do not allow for atrioventricular synchrony.

The sizes and designs of the studies were similar, as well. Each study evaluated the efficacy and safety of the pacemaker among the first 300 patients to complete 6 months of follow-up after the implantation procedure. During this follow-up period, additional patients under-

<table>
<thead>
<tr>
<th>Device</th>
<th>Size</th>
<th>Means of Fixation</th>
<th>Patients</th>
<th>Successful Implantation</th>
<th>Major Complications</th>
<th>Perforation or Effusion</th>
<th>Device Dislodgement</th>
<th>Adequate Pacing Measures at 6 Mo</th>
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</thead>
<tbody>
<tr>
<td>Nanostim</td>
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<td>Helical wire screw</td>
<td>526</td>
<td>95.8</td>
<td>6.5</td>
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<td>1.1</td>
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<tr>
<td>Micra</td>
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<td>Tines</td>
<td>725</td>
<td>99.2</td>
<td>4.0</td>
<td>1.6</td>
<td>0</td>
<td>98.3</td>
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* Data in the table pertain to the total cohort in each study, with the exception of the rates of adequate pacing measures at 6 months, which are for the cohort used in the primary efficacy analysis.