Refining the Standard of Care in Immune Thrombotic Thrombocytopenic Purpura

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Abstract: Acute immune thrombotic thrombocytopenic purpura (iTTP) is a medical emergency. In the setting of any thrombotic microangiopathy (TMA), blood should be drawn to measure ADAMTS13 activity and inhibitor levels, and an assessment should be made of TTP risk before receiving ADAMTS13 results. This can include the use of PLASMIC and French scores. Plasma exchange (PE) is then initiated. Upon confirmation of iTTP, with ADAMTS13 less than 10% in the presence of an inhibitor, interventions targeting all facets of iTTP pathophysiology should be instituted: replenishing ADAMTS13 via continued PE; suppressing anti-ADAMTS13 autoantibodies with glucocorticoids and rituximab; and inhibiting the thrombotic process—uncontrolled formation of platelet/Von Willebrand factor (VWF) microthrombi—with caplacizumab. The latter, an addition to existing standards of care, is based on International Society on Thrombosis and Haemostasis guidelines and emphasizes tracking of ADAMTS13 activity. In HERCULES, a pivotal randomized controlled trial, caplacizumab use resulted in fewer recurrent iTTP episodes, decreased PE, and shortened hospital stay. In settings of high suspicion for iTTP, clinicians should consider the administration of caplacizumab before receiving ADAMTS13 results because the greatest benefits of caplacizumab accrued starting it within 3 days of TMA recognition. In HERCULES, serious bleeding events occurred among 11% of those in the caplacizumab group vs 1% in the placebo group, but all resolved, most without intervention. iTTP survivors receiving PE and immunosuppression alone are at a heightened risk for stroke, other cardiovascular disorders, neurocognitive impairment, and kidney disease. Whether rapid prevention of VWF multimer/platelet formation with caplacizumab can suppress such long-term sequelae, and whether caplacizumab can replace PE in initial therapy, are under investigation.

Keywords
ADAMTS13, atypical hemolytic uremic syndrome, caplacizumab, plasma exchange, platelets, thrombotic thrombocytopenic purpura

Introduction

Thrombotic microangiopathy (TMA) includes thrombotic thrombocytopenic purpura (TTP), both the immune (iTTP) and congenital

Table 1. Clinical Prediction Tools to Help Distinguish TTP from aHUS and DIC: PLASMIC and French Scores[a]

Parameter[b]	French Score	PLASMIC Score
Platelet count <30,000/mm^3	1	1
Serum creatinine <2.26 mg/dL <2.0 mg/dL	 1 -	 - 1
Hemolysis	-	1
No active cancer in prior year	-	1
No history of solid organ or SCT	-	1
INR <1.5	-	1
MCV <90 fL	-	1
Positive ANA	1	-

aHUS, atypical hemolytic uremic syndrome; ANA, anti-nuclear antibody; DIC, disseminated intravascular coagulation; INR, international normalized ratio; MCV, mean corpuscular volume; SCT, stem cell transplant; TTP, thrombotic thrombocytopenic purpura.

[a]Highest likelihood of a TTP diagnosis is reflected by French scores of 2 to 3 and PLASMIC scores of 6 or greater. See the text for additional details concerning sensitivity and specificity.
[b]Hemolysis diagnosed by reticulocyte count greater than 2.5%, haptoglobin undetectable, or indirect bilirubin greater than 2.0 mg/dL.

Sources: Fage N et al. *Kidney Int Rep*. 2021;7(2):221-231[4] and Liu A et al. *Transfusion*. 2021;61(1):266-273.[5]

forms; atypical hemolytic uremic syndrome (aHUS); Shiga toxin-producing *Escherichia coli*-associated (STEC) HUS; and disseminated intravascular coagulation (DIC). The diagnosis of a TMA requires 3 components:

(1) Microangiopathic hemolytic anemia, including low haptoglobin, elevated lactate dehydrogenase, indirect bilirubin, and reticulocyte index; and recognition of fragmented red blood cells or schistocytes on peripheral blood smear or tissue biopsy in the absence of a positive direct Coombs test. Peripheral schistocytes may not be evident within the first few days of hemolytic anemia diagnosis owing to splenic sequestration and tissue extravasation; the peripheral smear must be examined daily.

(2) Thrombocytopenia, which differs in TTP vs aHUS, as detailed below.

(3) Organ dysfunction, the most common sites being the central nervous system (CNS), kidneys, cardiovascular system, and gastrointestinal tract in TTP, aHUS, and STEC-HUS, and in the lung in aHUS.[1]

DIC is a consumptive coagulopathy distinct from other TMAs, having prolonged prothrombin time and/or an elevated international normalized ratio and activated partial thromboplastin time. However, signs and symptoms of all 4 TMAs overlap extensively.

Distinguishing TTP From aHUS: Primary Considerations

Understanding the Pathophysiologic Differences Between TTP and aHUS is Critical to Establishing Effective Interventions

Upon recognizing a TMA and excluding DIC and, based on stool polymerase chain reaction and culture, STEC-HUS, plasma exchange (PE) should be initiated while awaiting a definitive diagnosis. The means to distinguish TTP from aHUS, using assays for Von Willebrand factor (VWF) cleaving protease, also known as ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), was identified almost 3 decades ago.[2] TTP is accompanied by a severe (<10% of normal) deficiency in plasma ADAMTS13 activity. When this deficit is related to an anti-ADAMTS13 autoantibody, it is known as immune TTP or acquired/autoimmune TTP. In rarer instances (<5% of cases), congenital mutations affecting both ADAMTS13 alleles are involved.

Following vascular injury in a healthy individual, VWF multimers, circulating in a coiled form, tether to newly exposed collagen. Under the stress of shear forces in microvessels, these multimers elongate, exposing sites capable of binding platelets and additional VWF. Thus, a platelet-rich plug is formed, upon which coagulation components are activated. This process is regulated by ADAMTS13, which cleaves elongated VWF to prevent unnecessary platelet aggregation. In the absence of ADAMTS13, uncontrolled propagation of platelet-VWF microthrombi occurs, with resultant tissue ischemia characteristic of TTP.[2]

In contrast, in aHUS, ADAMTS13 activity is often reduced from the normal range of 67% to 120%, but it typically remains greater than 5% to 10%.[1] In most aHUS cases, susceptibility to disease development is congenital rather than acquired, and is caused by mutations in

complement and complement regulatory proteins. Many prefer the term "complement-mediated HUS," rather than aHUS, to describe this type of TMA. Congenital mutations in complement proteins enable persistent overactivation of the alternative complement pathway once it has been triggered by certain conditions, including infection, pregnancy (the 2 most common initiating factors for aHUS), or other stimuli.[1,3] The ensuing generation of C5a (an anaphylatoxin) and C5b-9 (membrane attack complex) leads to inflammation, endothelial injury, platelet activation, thrombin generation, and propagation of fibrin-rich microthrombi.[1]

Clinical Prediction Tools: PLASMIC and French Scores

Both TTP and aHUS are associated with substantial and long-term morbidity and mortality unless promptly recognized and appropriately treated. Therefore, current International Society on Thrombosis and Haemostasis (ISTH) guidelines stress that patients should be assessed for the likelihood of a TTP diagnosis immediately upon recognition of a TMA. This assessment should be based on clinical judgment and risk assessment models, including the PLASMIC and French scores, while awaiting ADAMTS13 test results (Table 1).[4] This early assessment is important for 2 reasons. First, ADAMTS13 activity and inhibitor levels are often send-out tests, and results may not be available for 3 to 7 days. Second, in iTTP, disease control and survival are optimized when caplacizumab (Cablivi, Sanofi) is initiated within 3 days of TMA recognition, often before the receipt of ADAMTS13 test results.

The PLASMIC and French scores reflect pathophysiologic differences among the TMAs as follows:

(1) TTP is a platelet consumptive disorder with platelet-rich microthrombus formation. The median platelet count is 20,000/mm^3.[1] In aHUS, fibrin-rich microthrombi dominate, and thrombocytopenia is defined as a platelet count less than 150,000/mm^3 or less than 25% of baseline. Catastrophic aHUS can occur in the setting of platelet counts greater than 250,000/mm^3.[1]

(2) aHUS more frequently involves the kidneys.

(3) TMAs may be triggered by cancer, organ allografts, and hematopoietic stem cell transplants.

(4) Cobalamin C deficiency, with elevated mean corpuscular volume (MCV), may cause a TMA mimicking aHUS.

There are 7 components in the PLASMIC score and 3 components in the French score (Table 1).[4,5] The sensitivity for predicting TTP is very good for both scores, at 82.9% for the PLASMIC score and 72.2% for the French score for TMA patients between the ages of 18 and 39 years.[5] However, the specificity is superior with the French score vs the PLASMIC score, at 96% vs 80%, respectively, in the same age group.[5] Reliance on these tools is complicated by reduced sensitivity for patients aged 60 years and older, poor specificity in the setting of comorbidities, and predictive values calculated in TMA cohorts with a high iTTP prevalence.[4,5]

Biomarkers and Genetics

ADAMTS13 Activity. An ADAMTS13 activity level of less than 5% was originally required for a diagnosis of TTP.[6] However, levels of 5% to 10%, accompanied by clinical features of a TMA, have comparable specificity.[6] Some patients with intermediate activity levels of 10% to 20% that are accompanied by other features of TTP also respond to PE.[6]

Complement Proteins. All TMAs may be accompanied by complement activation. It is rare, however, for a TMA to be sustained by such activation alone unless it is poorly regulated, as in aHUS.[7-9] Therefore, measurement of circulating levels of standard complement components C3 and C4, or send-out tests for C5b-9 and MASP2 (a component of the lectin pathway of complement) are of limited value in TMA diagnosis, discriminating between iTTP and aHUS, and following disease activity. Exome sequencing and ultrafast genome sequencing for complement mutations can help distinguish aHUS from other TMAs[10]; however, pathogenic mutations or variants of unknown significance that are likely to be pathogenic have been identified in only about 70% of aHUS cases responsive to anti-C5 therapy.[1,3,11] Despite promising leads,[12] there are currently no biomarkers with validated utility in assisting in the diagnosis of an aHUS type of TMA. C5b-9 deposition on the microvasculature in biopsies of normal-appearing skin[13] or involved kidneys[14] is prominent in aHUS and not iTTP, but its sensitivity and specificity in defining TMA type has not been established.

Limitations of PE in Treating TMAs

Prior to late 2011, when the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the anti-C5 monoclonal antibody eculizumab (Soliris, Alexion/AstraZeneca) for aHUS, PE and plasma infusion (PI) were used to manage both aHUS and iTTP. There are no prospective clinical trials showing the efficacy of plasma in the former. PE/PI does not influence complement dysregulation at the tissue level and does not prevent clinical progression.[1,15] The failure to recognize a meaningful response to therapeutic intervention in aHUS—still misunderstood among many non-TMA specialists—is based on a dichotomy between treatments that ameliorate clinical laboratory abnormalities and those that affect underlying pathophysiology. Specifically, the use of PE in most forms of aHUS is primarily a temporizing measure:

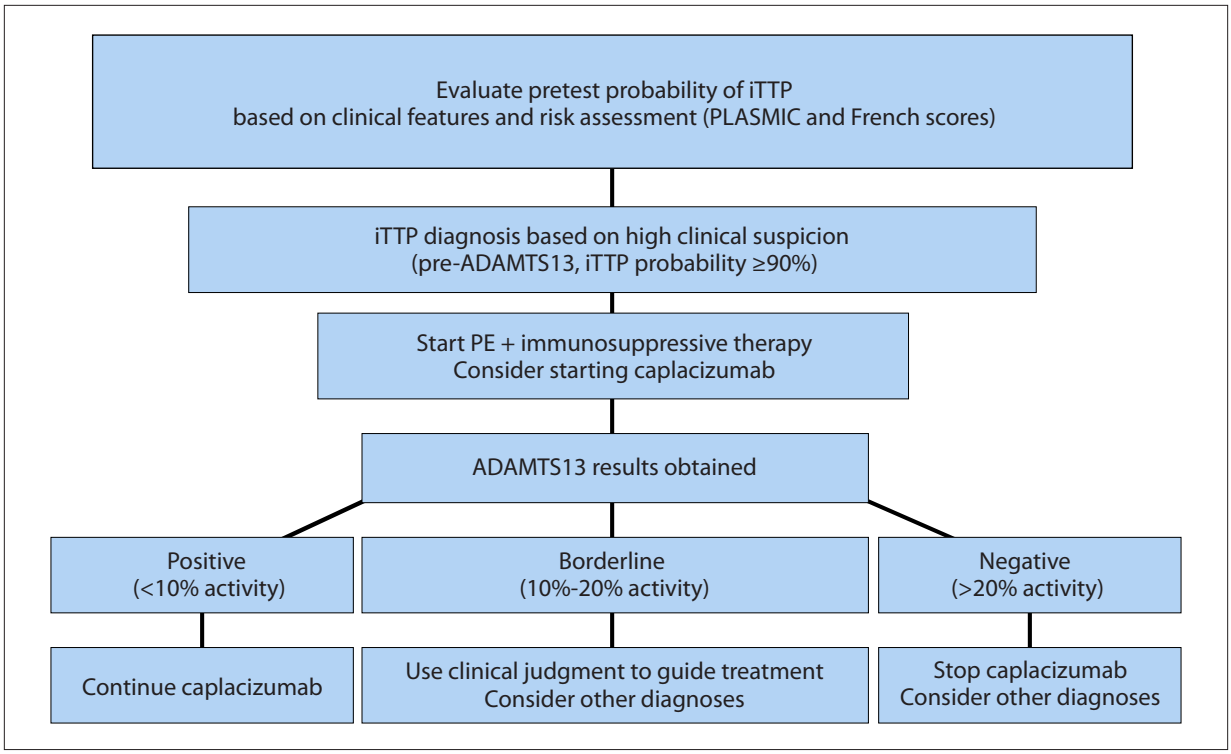

Figure. Guidelines for the use of caplacizumab in iTTP. The International Society on Thrombosis and Haemostasis has established guidelines for the use of caplacizumab in patients with acute TMA. This chart provides details for those individuals diagnosed with a TMA and with a high suspicion of iTTP, based on clinical signs and PLASMIC or French scores, for whom ADAMTS13 results are available within 7 days of a TMA diagnosis.
iTTP, immune thrombotic thrombocytic purpura; PE, plasma exchange; TMA, thrombotic microangiopathy.

the hematologic features of a TMA may resolve, but it has no impact on survival or morbidity.[16] This likely relates to the frequency of complement mutations underlying the disorder.[1] Fresh frozen plasma (FFP) contains complement factor H (CFH) and complement factor I, the 2 most commonly mutated complement regulatory proteins in aHUS; infusion of these factors likely subserves PE-associated responses.[16,17] The risk of end-stage renal disease and death is not altered, however, because tissue damage persists. The normalization of platelet counts following PE in aHUS does not block platelet activation, with continued high expression of P-selectin[18] and progressive renal injury.[19] Inhibition of terminal complement components is required. As detailed below, a similar concept applies to the use of PE in iTTP, and PE is often only a temporizing measure. PE does markedly improve initial survival rates, but iTTP is more than an acute disorder. Long-term CNS, cardiovascular, and renal sequelae occur in some 40% of patients following recovery from an acute episode.[20]

Guidelines for the Use of PE in aHUS

The above considerations have informed the American Society for Apheresis (ASFA) guidelines for the use of PE in aHUS.[21] A rare form of autoimmune aHUS involving anti-CFH autoantibodies, often coupled to complement mutations (a disorder referred to as deficiency of CFHR plasma proteins),[22,23] has received a category I recommendation, which is the highest category. In contrast, for TMAs known to be linked to complement mutations—one classic definition of non-immune aHUS—PE has received a category III recommendation and the statement that the "[o]ptimum role of apheresis therapy is not established." I have advocated against the use of PE in non-autoimmune aHUS, for clinical and economic considerations.[1,24]

Guidelines for the Use of PE in iTTP

In stark contrast to the recommendations for PE in non–autoantibody-associated aHUS, the use of PE in iTTP is clear, receiving a category I with the strongest grade of recommendation, 1A, based on "high-quality evidence and randomized clinical trials."[21] This is logical because FFP contains significant amounts of ADAMTS13, the enzyme whose activity is suppressed in TTP. Indeed, iTTP-linked mortality declined from more than 90% to less than 10%

with the institution of therapeutic PE.[25] The efficacy of PIs alone was first recognized in 1977. Fourteen years later, PE rather than PI became the standard of care based on a prospective randomized trial.[25] If an apheresis station was not immediately available and renal function permitted, FFP infusions were advised while awaiting PE.[26] However, in the initial study of PE vs PI, the total volume of plasma received by patients undergoing PE was 3-fold greater than that received by those undergoing PI.[25] That trial was not designed to determine whether the superiority of PE—a complete platelet response of 47% and a survival rate of 96% at the conclusion of the first treatment cycle vs a complete platelet response of 25% and a survival rate of 84% in the PI group—was attributable to the removal of harmful substances or to administration of plasma in larger volumes than was possible with PI.[25] Utilizing PE, the mean time to resolution of neurologic changes was 3 days, to a normal lactate dehydrogenase level was 5 days, to a normal platelet count was 10 days, and to a decrease in serum creatinine of at least 25% from baseline was 15 days.[26]

Subsequently, some case reports showed that plasmapheresis and replacement with albumin and saline, rather than with plasma, was ineffective in iTTP,[27] and a direct pathogenic role for anti-ADAMTS13 antibodies was documented using nonhuman primate and rodent models.[28,29] Plasmapheresis also does not significantly reduce anti-ADAMTS13 autoantibodies, which are primarily of the immunoglobulin G (IgG) isotype and not easily removed compared with antibodies of IgM isotype; however, plasmapheresis can deplete large VWF multimers and ADAMTS13 immune complexes.[6] This further supports the benefit of PI alone as an initial intervention.

Over the next 2 decades, there were few therapeutic advances in the treatment of iTTP. The use of FFP depleted of high molecular weight VWF multimers in the form of cryo-poor plasma or cryosupernatant was suggested, but there is no conclusive evidence for its efficacy over standard FFP.[6] In addition, increasing the frequency of PE to twice daily does not improve complete response (CR) rates.[30] In the absence of CNS hemorrhage, supportive platelet transfusions should be avoided. This is less over concern that platelet transfusions will initiate an acute myocardial infarction or stroke—seen in case reports and thought logical, given that TTP, as aHUS, occurs in the setting of platelet activation, but not supported by systematic reviews—and more because they are ineffective in advancing hemostasis.[31] The important caveat in the ASFA guidelines for iTTP treatment is a qualification to their highest (category I) recommendation: the use of PE is advised as a "primary standalone" treatment or "in conjunction with other modes of treatment." In fact, advances in the detection, management, and monitoring of iTTP indicate a need to revise what was previously accepted as the standard of care for this disorder.

Understanding the Limits of PE in iTTP

Traditionally, remission in iTTP has been defined as the resolution of clinical symptoms and maintenance of a normal platelet count for at least 30 days after the last PE and completion of a corticosteroid taper, if used.[30] The recurrence of clinical symptoms or thrombocytopenia before this 30-day interval defined "inadequate treatment." However, some 40% of iTTP patients treated with PE/corticosteroids and in CR, based on platelet count and clinical signs, had a return of ADAMTS13 suppression with the reemergence of ADAMTS13 autoantibodies, likely related to B-cell reconstitution and/or persistence of plasma cells.[32] In those for whom ADAMTS13 activity was greater than 15%, this rate was only 5%.[2] Relapse has been linked to the reemergence of autoantibodies recognizing their original anti-ADAMTS13 targets—usually in cysteine-rich/spacer domains of the enzyme—or autoantibodies directed against new epitopes.[2] "Refractory" disease, with no or only transient response in platelet count or continued clinical deterioration despite the use of PE and corticosteroids,[30] was another issue. Immunosuppressive regimens were empirically used in refractory disease, including splenectomy, cyclophosphamide, vincristine, cyclosporine, and the anti-CD20 monoclonal antibody rituximab.[30]

Once it was established that rituximab could facilitate the resolution of iTTP, reducing the number of PEs required to achieve a CR and decreasing the 1-year relapse rate, it was recommended for preemptive use in patients with persistent severe (<10%) ADAMTS13 deficiency during iTTP remission.[32] The fact that the number of initial PEs required to achieve a CR was thereby also reduced, along with the need for subsequent PEs on disease relapse, is significant for 2 reasons. First, plasma is a limited resource, and second, complications—including death related to sepsis and hemorrhage attendant on central venous catheter use, and serum sickness—occurred in a quarter of patients receiving PE.[33] In a prospective study with 7 years of follow-up, rituximab reduced clinical relapses from 74% to 0%.[34] Furthermore, the rituximab dosing regimen of 375 mg/m^2 weekly for 4 weeks, which is based on non-Hodgkin lymphoma protocols, may not be required in iTTP when used with PE and corticosteroids. This was suggested by a prospective phase 2 trial of iTTP patients treated with rituximab at 100 mg every 5 to 9 days for 4 weeks.[35] However, studies to establish whether this low dose diminishes long-term response durability are required.

Table 2. A New Triplex Therapy for iTTP Based on Induction of a Biological, Not Only Clinical, Remission

iTTP Pathogenesis	Intervention	Strategy
Low ADAMTS13 activity leading to uncontrolled propagation of micro-thrombi formed by VWF multimer/platelet complexes	Augment ADAMTS13 levels	Plasma exchange: FFP contains ADAMTS13
Anti-ADAMTS13 autoantibodies suppress activity of this VWF cleaving protease	Block autoantibody production	Immune suppression: typically with prednisone plus rituximab
Persistent microthrombi formation related to VWF multimer/platelet interactions	Block platelet binding to VWF multimers	Caplacizumab: binds to the A1 domain of VWF, preventing interaction with platelet glycoprotein Ib-IX-V receptor

FFP, fresh frozen plasma; iTTP, immune thrombotic thrombocytopenic purpura; VWF, Von Willebrand factor.

Are PE Plus Corticosteroids/Rituximab Sufficient to Control iTTP?

Frequent relapses and refractory disease despite PE and preemptive immunosuppression highlighted the need for "a more personalized strategy,"[34] based on disease pathophysiology. First, there were no clear parameters to identify which patients were at risk of early relapse or failure to respond to PE and immunosuppression, although Black Caribbean ethnicity appears to be a strong risk factor for relapse.[36] Second, the optimal ADAMTS13 monitoring interval and the length of time required to maintain such surveillance are unclear.[36] Third, although it is gratifying that patients continue to respond to repeat courses of rituximab in iTTP relapse and infectious complications are uncommon,[36] optimal alternative interventions for patients experiencing multiple relapses using rituximab are unknown. Other anti-CD20 agents, including obinutuzumab (Gazyva, Genentech) and ofatumumab (Arzerra, Novartis), as well as proteasome inhibitors such as bortezomib, have been used.[36,37]

Long-Term Sequelae Following Induction of a CR With PE and Immunosuppression

iTTP survivors are at risk for myriad adverse health outcomes, including higher than expected rates of stroke, other cardiovascular disease, neurocognitive impairment, depression, hypertension, and kidney disease.[20,38,39] The association of silent cerebral infarction, detected by brain magnetic resonance imaging (MRI), with impaired cognition in these individuals "suggests that these silent infarcts are neither silent nor innocuous."[38] The fact that those in CR characterized by ADAMTS13 activity in the lowest quartile of the normal range (ie, ≥60% but <80%) had a 2-fold higher risk of stroke than those in the highest quartile suggests that ADAMTS13 has important physiologic antithrombotic functions.[40] This may also account for subclinical myocardial damage in iTTP survivors, detected by stress cardiac MRI.[39] Many patients do not recover plasma ADAMTS13 activity to more than 20% even weeks following combination treatment with PE, corticosteroids, and rituximab.[41] In one series, some 15% of patients had ADAMTS13 activity of less than 10% despite achieving normalization of platelet count.[41]

Recognition of a Requirement for a New Standard of Care in iTTP

The above issues illuminated the need for additional interventions to block VWF multimer/platelet aggregation very early in the disease course, rather than waiting days for ADAMTS13 replacement via PE/PI to take effect, and weeks to months for immunosuppressive regimens to inhibit anti-ADAMTS13 antibody production. iTTP pathophysiology suggested 2 potential points for a companion intervention to PE plus immunosuppression. One involves N-acetylcysteine (NAC), which is FDA-approved in chronic obstructive lung disease to reduce mucin multimers. Because VWF polymerizes in a manner similar to mucin, acting via C-terminal disulfide bonds that join through their N termini by further disulfide binding, it was unsurprising that NAC blocked VWF multimer formation and platelet aggregation in vitro and in mouse models, and might have a role in TTP therapeutics.[42] There are case reports of dramatic responses to NAC used in high doses in patients with refractory[43] and relapsed refractory[44] iTTP, but no clinical trials to date. The other intervention point involves caplacizumab.

Upfront Use of PE, Corticosteroids/Rituximab, and Caplacizumab in iTTP

Caplacizumab suppresses VWF multimer/platelet aggregation in a manner distinct from NAC. It is a small (molecular weight, 28kDa) anti-VWF humanized single-domain immunoglobulin or "nanobody," originally produced in llamas and now in *E. coli* by recombinant DNA technology. It binds with high affinity to the A1

domain of VWF, preventing its interaction with the platelet glycoprotein Ib-IX-V receptor. It was approved by the EMA in 2018 and by the FDA in February 2019 for use in iTTP in conjunction with PE and immunosuppression. Approval was based on HERCULES, a randomized, double-blind, placebo-controlled trial of 145 patients with iTTP.[45] All received PE and prednisone (1 mg/kg daily), and 48% in the placebo group and 39% in the caplacizumab group also received rituximab. Those assigned caplacizumab were administered a 10-mg intravenous loading bolus followed by 10 mg daily subcutaneously (SC) during PE and for 30 days. The decrease in median time to normalization of the platelet count, at 2.69 vs 2.88 days, was statistically significant (P=.001). The reduction was only 4.5 hours, and there was only a trend to suppression of refractory disease in this early protocol study, but there was impressive improvement in many clinically relevant outcomes:

(1) a 74% decrease in the composite endpoint (major thromboembolic events, iTTP recurrence, and death; P<.001);

(2) a decrease in the percentage of patients having an iTTP recurrence, at 12% vs 38% (P<.001);

(3) a 38% shorter duration of PE use, at 5.8 days vs 9.4 days, and a reduction in plasma volume, at 21.3 L vs 35.9 L;

(4) a 65% shorter duration of care in the intensive care unit setting, at a mean of 3.4 vs 9.7 days; and

(5) a 31% shorter duration of hospitalization, at 9.9 vs 14.4 days.

Combining the results of HERCULES with those of TITAN, an earlier randomized controlled study of caplacizumab,[46] uncovered only 1 TTP-related fatality among 108 patients in the drug arms vs 5 of 112 in the control arms.[47] Supported by data from these trials, an international working group revised definitions of iTTP remission and relapse, originally based primarily on platelet count, to include a more clinically meaningful outcome: a "biological remission" characterized by partial or complete restoration of ADAMTS13 activity.[47,49]

Serious Adverse Events

Serious adverse bleeding events occurred in 11% of patients in the caplacizumab group vs 1% of those in the placebo group in the HERCULES trial. All events resolved, most without intervention. This was not unexpected but rather an extension of the therapeutic effect of caplacizumab with the potential for a Von Willebrand disease–like mucocutaneous bleed. Over 3 years of HERCULES follow-up, there were no new safety concerns, and no boosting of antidrug antibodies occurred with repeat administration of caplacizumab for iTTP recurrences.[48]

Real-World Experience With Caplacizumab

Multiple "real-world" trials confirmed the results of the TITAN and HERCULES studies and the superiority of a triplet regimen—PE, immunosuppression with glucocorticoids and rituximab, and caplacizumab—targeting all 3 key points of iTTP pathophysiology (Table 2), as frontline therapy. Those included cohorts in France,[50] the United Kingdom,[51] and Spain.[52] A 10-country European observational cohort, Capla 500, encompassed 942 patients treated with caplacizumab and 492 historical controls treated without caplacizumab.[53] (Corticosteroids were used in 99% and 93%, and rituximab in 92% and 71%, respectively.) It documented that calacizumab:

(1) was feasible to start within 3 days of TMA diagnosis, recognized by the first day of PE, in 76% of patients;

(2) was superior to the standard of care regardless of the time of initiation after PE, with a 5-fold higher success rate than controls in achieving a CR (P<.0001);

(3) required fewer PEs and resulted in fewer exacerbations or refractory periods regardless of rituximab use (P<.0001 for all);

(4) shortened time to achieving an increase in ADAMTS13 activity to at least 20%; and

(5) increased 3-month survival after first PE: 98.6% vs 93.3% (P<.0001).

Potential Issues With Caplacizumab Use

There are several potential issues with the use of caplacizumab. First, a caveat raised by the French cohort was the occurrence of thromboembolic events in 12% of caplacizumab patients, including pulmonary embolism, deep vein thrombosis, and catheter-associated thrombosis.[50] However, such large vessel events are not part of iTTP pathology—it is a microvascular process—and all occurred in individuals who did not receive thromboprophylaxis despite platelet counts rising to more than 50,000/mm^3. It was speculated that clinicians were concerned about the potential risks of combining thromboprophylaxis with caplacizumab.[50] The study authors concluded that standard prophylaxis should be used, especially with platelet levels greater than 50,000/mm^3. Indeed, concomitant use of low molecular weight heparin with caplacizumab showed no risk of increased bleeding in other iTTP cohorts,[54] although additional real-world data are required in terms of its use with antiplatelet agents.

Second, a meta-analysis of 5 studies failed to document a reduction in the relative risk of death with the addition of caplacizumab to PE and immunosuppression and found an increase in the risk of iTTP relapse.[55] However, these "relapses" were reclassified as exacerbations because treatment was discontinued before establishing ADAMTS13 activity levels of 10% or greater.[56] In

HERCULES, investigators could continue caplacizumab for an additional 28 days following the standard 30-day dosing schedule after PE if ADAMTS13 activity had not recovered to at least 10%. With that proviso, there were no exacerbations or relapses.[56]

Third, 28% of patients in a UK cohort treated with caplacizumab following the 30-day (plus 28 days if necessary) HERCULES regimen had a significant delay in achieving ADAMTS13 activity greater than 30%.[57] However, no plausible hypothesis was offered as to why this had occurred, nor has it been reported in other studies.[53] In the much larger Capla 500 cohort, the time to ADAMTS13 recovery to at least 20% was lower in the caplacizumab vs controls (P=.01), although a relationship with differential rituximab exposure in the 2 cohorts cannot be excluded.[53]

New ISTH Guidelines Highlight the Importance of Caplacizumab in iTTP

The Figure outlines ISTH 2020 guidelines for caplacizumab use in settings with a high probability of an iTTP diagnosis based on clinical suspicion, including the use of PLASMIC and French scores, when ADAMTS13 test results can be obtained within 7 days.[58] Specifically:

(1) caplacizumab is recommended for acute iTTP (first event or relapse) with "moderate clinical certainty";

(2) the greatest benefit is accrued if caplacizumab is started at time of TMA recognition. Clinicians should consider administration of the drug even before results of ADAMTS13 activity are available; and

(3) discontinuation of caplacizumab after platelet count normalization but with ADAMTS13 activity of less than 10% may result in disease exacerbation.

On day 1, an 11-mg bolus intravenous injection is administered at least 15 minutes before PE, followed by a second 11-mg SC injection after PE completion. An 11-mg SC dose is then used after each daily PE, and daily for 30 days after stopping PE. (A single dose is here given as 11 mg, not 10 mg as stated in HERCULES and TITAN. This is based on demonstration that extraction of drug from each vial yields 11 mg, not 10 mg.) If signs of TMA persist, or ADAMTS13 activity remains less than 20%, treatment extension up to 28 days may be utilized.

Postmarketing studies found an increased risk of bleeding in individuals with underlying coagulopathies and in concomitant use with anticoagulants or antiplatelet agents. This issue was discussed in more detail above. It was also recommended that caplacizumab should be held for 7 days before elective surgery, dental procedures, or other invasive interventions, recognizing that this will increase the risk for iTTP exacerbation if ADAMTS13 activity has not recovered. In that case, resumption of PE may be required. If clinically significant bleeding occurs, caplacizumab should be interrupted and VWF concentrate or VWF complex (Humate-P, CSL Behring) should be used to achieve hemostasis.

Treating iTTP in Pregnancy

Pregnancy, including the postpartum period (≤3 months after delivery), is a risk factor for an initial or recurrent episode of both congenital and immune TTP.[59] The likelihood of having a congenital form is much higher (24%-66%) than expected in adult-onset TTP in general (<5%). In the setting of congenital ADAMTS13 deficiency, the incidence of TTP during pregnancy approaches 100%, accompanied by a high rate of fetal loss.[59,60] One reason for this association is the excess production of VWF multimers in pregnancy. Levels peak in the third trimester, followed by a gradual normalization 4 to 6 weeks postpartum.[59]

Management of iTTP in pregnancy involves PE and corticosteroids (prednisone rather than dexamethasone, as the former does not cross the placenta). Rituximab is avoided based on a lack of safety data, although it has been employed in life-threatening gravidic iTTP.[59] There are no published data to assess the risk/benefit profile of caplacizumab use in this setting.

It is also critical to consider alternative diagnoses in pregnancy-linked TMAs, including hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and "postpartum HELLP," often an aHUS-type of TMA.[1] The only TMA to occur most frequently postpartum is aHUS, complicating some 1 in 25,000 pregnancies.[61,62] It is treated with eculizumab. Ravulizumab (Ultomiris, Alexion/AstraZeneca), the long-acting form of this drug, is also efficacious, although with much less safety data than for eculizumab in this setting.[62]

Monitoring for iTTP Relapse

Close follow-up based on ADAMTS13 activity and inhibitor levels is important because it focuses on the pathogenesis of iTTP, the formation of ADAMTS13 autoantibodies. However, such monitoring schemes fail to incorporate clinical signs and symptoms. The gap between the first observation of ADAMTS13 activity of less than 10% after a CR vs the first relapse based on platelet counts and/or clinical symptoms can be huge and unpredictable, from 0.3 to 9.5 years.[63] In the UK review, 40% of those with ADAMTS13-based relapses were symptomatic, primarily new-onset lethargy and headache.[56] It has been suggested that earlier intervention for disease relapse should be based on symptoms in addition to ADAMTS13 activity thresholds. In congenital TTP, disease onset is heralded by lethargy in 19% of patients and headache in 23%, with ADAMTS13 replacement

ameliorating these symptoms in 88% of patients.[64]

There are no explicit guidelines as to the optimal frequency of ADAMTS13 monitoring; the US Thrombotic Microangiopathy Alliance recommends testing every 3 months after remission.[65] In association with caplacizumab, I also obtain ADAMTS13 activity weekly and at the final dose of the drug.

Economic Considerations in Utilization of Caplacizumab in iTTP

James N. George, MD, the founder of the Oklahoma TTP Registry, speculated that the principal reason for not using caplacizumab in the initial treatment of iTTP is expense, with a single dose costing $8000 and a 30-day regimen costing $240,000.[66] However, those numbers do not take into account that the greatest benefit is realized when caplacizumab is used early in the disease course, ideally at the time of TMA diagnosis, and that PE can be discontinued once the platelet count begins to recover, as disease exacerbation rarely occurs while caplacizumab is continued.[67] The drug can also be self-administered at home, unlike PE. In addition, almost 60% of iTTP patients receiving caplacizumab required treatment for less than 30 days, resulting in cost savings.[68] A recent analysis documented its cost effectiveness in both the European and US markets,[69] with prices falling within the $195,300 "willingness to pay threshold" set by the US Congress.[70]

Future Issues in iTTP Management

Numerous questions remain to be answered regarding the management of patients with iTTP:

(1) What is the optimal time frame for serial ADAMTS13 assessment? Should it be personalized, recognizing certain groups at high risk for relapse?

(2) What is an optimal level of circulating ADAMTS13, below which immune suppressive therapy with repeat courses of rituximab or other immunomodulatory agents should be initiated? Many observational studies suggest a cutoff of 20% to 30%; others suggest that the optimal level in terms of obviating long-term sequelae is one within the normal range (ie, >60-80%).[40]

(3) What is the best means to suppress or eradicate ADAMTS13 autoantibodies in those who do not respond to rituximab?

(4) Will early intervention with caplacizumab, in conjunction with PE and corticosteroids/rituximab, and close ADAMTS13 follow-up, preclude long-term sequelae and prolong overall survival to an even greater extent than shown in early observational cohorts?

(5) Could caplacizumab replace PE in initial iTTP therapy, as suggested by a recent retrospective study,[71] and the aim of an ongoing phase 3 trial?[72] As one expert noted, this would simply substitute one temporizing treatment for another, but one that is simpler, perhaps safer, and capable of intervening much faster in disease pathogenesis.[66]

(6) Could other agents assist in optimizing iTTP treatment, such as recombinant ADAMTS13 and Microlyse, a thrombolytic that targets VWF and degrades microthrombi?[6]

Conclusion

Acute iTTP is a medical emergency that requires prompt recognition and pathophysiology-guided management. In the setting of any thrombotic microangiopathy, blood should be drawn to assess ADAMTS13 activity and inhibitor levels, and the PLASMIC and French scores should be calculated. PE or, if an apheresis station is not immediately accessible, PI should be instituted while awaiting ADAMTS13 results. In situations with a high clinical suspicion of iTTP, particularly with an elevated PLASMIC score (≥6) or French score (≥2), consider concomitant administration of corticosteroids and rituximab, and consider initiation of caplacizumab within 3 days if ADAMTS13 levels have not yet returned, in expectation of confirming an iTTP diagnosis. When the triplex of PE, corticosteroids/rituximab, and caplacizumab is used on initial recognition of iTTP, PE can be discontinued once the platelet count begins to recover. Disease exacerbation rarely occurs during caplacizumab administration. It is reasonable to anticipate that caplacizumab could replace PE in the initial treatment of iTTP based on recent controlled and real-world studies. Finally, because iTTP survivors treated with PE plus corticosteroids/rituximab are at risk for myriad adverse health outcomes, researchers are investigating whether intervention with caplacizumab at the time of iTTP diagnosis to rapidly prevent VWF multimer-platelet microthrombi could lower this risk.

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