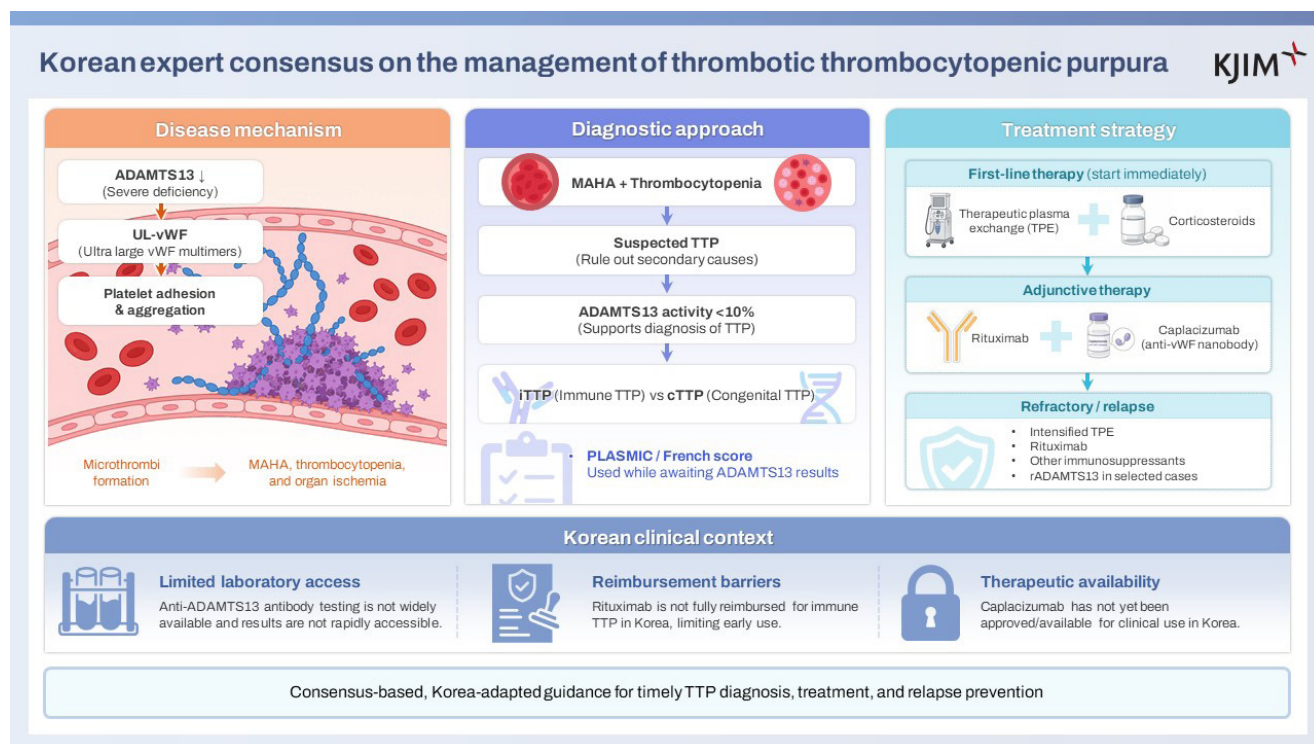


Korean expert consensus on the management of thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening thrombotic microangiopathy resulting from severe ADAMTS13 deficiency. Although effective treatments, such as therapeutic plasma exchange, immunosuppressive therapy with rituximab, and caplacizumab, have significantly improved survival, important challenges remain. These include limited diagnostic capacity, barriers to the early use of novel therapies, and long-term complications. In Korea, additional difficulties persist due to the restricted availability of ADAMTS13 antibody testing, reimbursement limitations for rituximab, and the absence of caplacizumab in clinical practice. To address these issues, the Korean Society of Hematology Thrombosis and Hemostasis Working Party convened an expert panel to develop consensus recommendations for the diagnosis and management of TTP. The panel reviewed current international guidelines, pivotal clinical studies, and real-world experiences and adapted them to the Korean clinical setting. This consensus statement provides updated recommendations for diagnostic approaches, initial and adjunctive therapies, management of refractory disease, ADAMTS13 monitoring, and long-term follow-up. By integrating international evidence with local circumstances, this document aims to provide Korean clinicians with practical, up-to-date guidance to enhance the routine care of patients with TTP.

Keywords: Thrombotic thrombocytopenic purpura; Diagnosis; Therapy; Consensus; Korea

INTRODUCTION

Thrombotic microangiopathy (TMA) is a heterogeneous group of syndromes characterized by endothelial injury and thrombotic occlusion of the microvasculature, leading to microangiopathic hemolytic anemia (MAHA), consumptive thrombocytopenia, and ischemic organ damage [1]. Representative disorders within the TMA spectrum include thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and secondary TMA.

TMA presents with diverse and complex clinical manifestations, which often hinder prompt diagnosis. It should be suspected when thrombocytopenia and MAHA are identified in laboratory findings. Once TMA is confirmed, it is crucial to differentiate among TTP, Shiga toxin-producing *Escherichia coli*-HUS, atypical HUS (aHUS), and secondary TMA. Traditionally, MAHA, thrombocytopenia, and acute kidney injury have been considered the clinical triad of HUS, while the addition of fever and neurological abnormalities forms the classic pentad of TTP. However, not all patients exhibit these classical symptoms, and clinical presentation varies among individuals, making the differentiation of TMA subtypes challenging [1,2].

TTP is an acute, life-threatening TMA resulting from severe deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), a plasma metalloprotease that cleaves ultra-large multimers of von Willebrand factor (vWF). ADAMTS13 deficiency re-

sults in the accumulation of unusually large vWF multimers in the circulation, promoting platelet adhesion, aggregation, and microthrombus formation within small arterioles and capillaries [2-4]. TTP is classified according to the underlying cause of ADAMTS13 deficiency into immune TTP (iTTP or acquired TTP) and congenital TTP (cTTP or Upshaw-Shulman syndrome). iTTP is an autoimmune disorder caused by the production of autoantibodies against ADAMTS13, whereas cTTP is a rare autosomal recessive disorder resulting from mutations in the *ADAMTS13* gene and accounts for approximately 3–5% of all TTP cases [2,5,6]. Clinically, iTTP typically presents as an acute disease in adults, whereas cTTP is more commonly diagnosed during the neonatal period, childhood, or pregnancy. Thus, age at onset, particularly neonatal presentation or manifestation during pregnancy, provides important clues for the initial differential diagnosis. Even when ADAMTS13 deficiency is congenital, TTP symptoms may occur intermittently, indicating that additional triggers are required to induce disease flares.

Recent advances have substantially improved our understanding of the pathophysiology of TTP, and these insights have been successfully translated into patient management. Given these developments, there is a clear need to establish Korean guidelines for the diagnosis and management of TTP that reflect the local clinical context. Therefore, expert physicians from the Korean Society of Hematology Thrombosis and Hemostasis Working Party initiated the development of a consensus statement on the diagnosis and

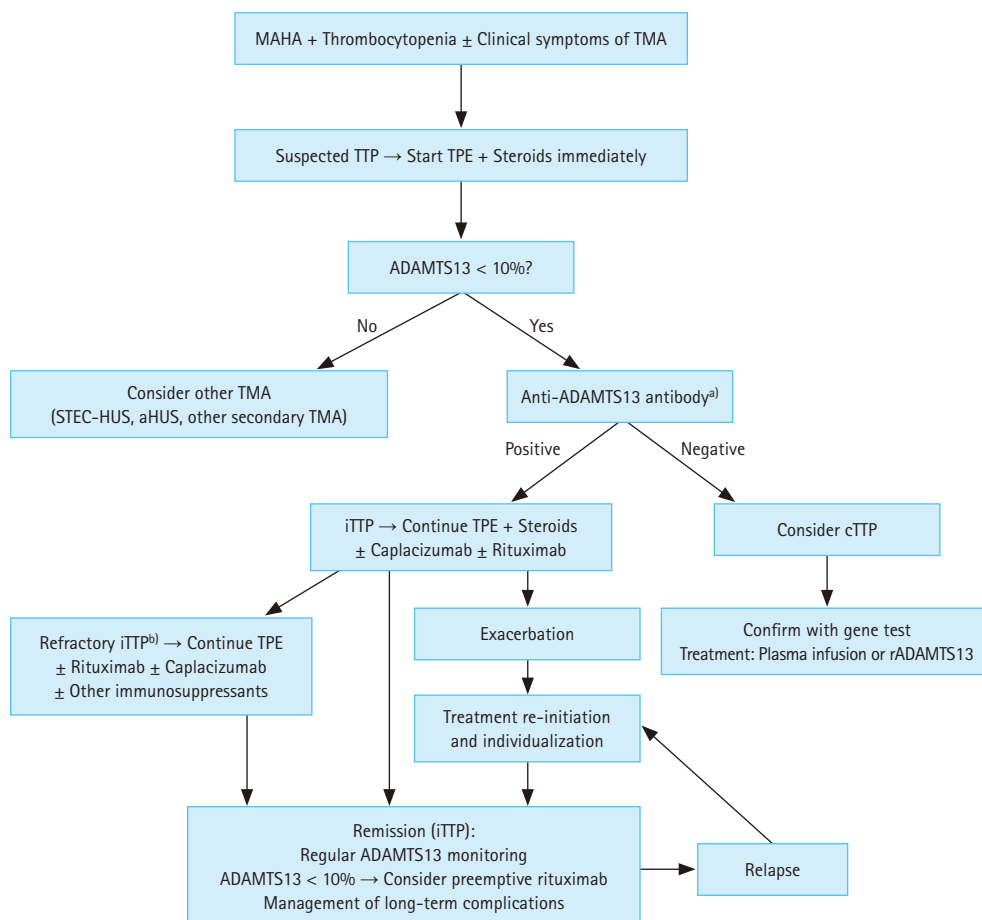


Figure 1. Diagnostic and therapeutic algorithm for the management of thrombotic thrombocytopenic purpura. MAHA, microangiopathic hemolytic anemia; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; TPE, therapeutic plasma exchange; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; STEC-HUS, Shiga toxin-producing *Escherichia coli*-hemolytic uremic syndrome; aHUS, atypical hemolytic uremic syndrome; iTTP, immune TTP; cTTP, congenital TTP; rADAMTS13, recombinant ADAMTS13. ^{a)}Anti-ADAMTS13 antibody testing may be unavailable in routine clinical practice in Korea. Moreover, a negative antibody result does not completely exclude iTTP, particularly during the acute phase. ^{b)}In refractory iTTP, rituximab should be considered if not previously administered. Caplacizumab may be used, although its efficacy appears limited in the salvage setting. Other immunosuppressive agents can also be considered as salvage therapy.

management of TTP. Specific topics related to TTP management were assigned to individual members, who drafted sections of the manuscript based on recent international guidelines and pivotal clinical trials. The initial draft was independently reviewed by additional members, followed by multiple rounds of revision and collective evaluation. To provide an overarching framework for the diagnostic and therapeutic approaches discussed in this consensus, a schematic algorithm for TTP management is presented (Fig. 1). This figure illustrates the internationally recognized diagnostic and treatment pathway; however, its application in Korea should be adapted according to the local availability

of diagnostic assays and therapeutic agents, including anti-ADAMTS13 antibody testing and caplacizumab.

DIAGNOSIS

Assessment of ADAMTS13 activity should be performed in all patients with unexplained thrombocytopenia and MAHA, regardless of accompanying symptoms. TTP is diagnosed when ADAMTS13 activity is less than 10%. Blood samples should ideally be collected before initiating plasma exchange therapy to ensure accurate measurement [2].

Table 1. Clinical scoring systems to estimate the probability of severe ADAMTS13 deficiency in patients with TMA

	French score [11]	PLASMIC score [12]
Platelet count	$\leq 30 \times 10^9/L$: +1	$< 30 \times 10^9/L$: +1
Creatinine level	≤ 2.26 mg/dL: +1	< 2.0 mg/dL: +1
Hemolysis variable ^{a)}		+1
No active cancer		+1
No history of solid-organ or stem-cell transplantation		+1
MCV < 90 fL		+1
INR < 1.5		+1
ANA	+1	
Total score and likelihood of TTP	0: 2% 1: 70% 2–3: 94%	0–4 (low risk): 0–4% 5 (intermediate risk): 9–24% 6–7 (high risk): 62–82%

ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; TMA, thrombotic microangiopathy; MCV, mean corpuscular volume; INR, international normalized ratio; ANA, antinuclear antibody; TTP, thrombotic thrombocytopenic purpura.

^{a)}Reticulocyte count $> 2.5\%$, undetectable haptoglobin, or indirect bilirubin > 2.0 mg/dL.

Other TMAs, including aHUS, should be considered in Shiga toxin–negative patients with normal ADAMTS13 activity ($\geq 10\%$) [2,7].

When severe ADAMTS13 deficiency is confirmed, subsequent evaluation should determine the underlying mechanism. The detection of anti-ADAMTS13 antibodies confirms a diagnosis of iTTP. However, the anti-ADAMTS13 inhibitor assay has not yet been approved for clinical use in Korea and is currently available only for research purposes, which limits its accessibility in routine practice. In patients with persistent severe ADAMTS13 deficiency and no detectable anti-ADAMTS13 antibodies during remission, *ADAMTS13* gene sequencing should be performed to rule out cTTP [2,7].

The clinical presentation of iTTP is typically acute and characterized by MAHA and severe thrombocytopenia [8]. Prodromal symptoms such as fatigue, arthralgia, myalgia, and abdominal or lumbar pain may precede diagnosis [9]. The classic pentad—thrombocytopenia, MAHA, fever, neurological abnormalities, and renal dysfunction—is rarely observed in its entirety. Neurological symptoms occur in 50–80% of patients and range from headache and confusion to seizures, focal neurological deficits, altered mental status, and even coma [2]. Cardiac involvement, often indicated by elevated troponin levels, is common and associated with poor outcomes [10].

Laboratory findings typically reveal severe thrombocytopenia (usually $\leq 30,000/\text{mm}^3$) and evidence of MAHA,

including elevated lactate dehydrogenase (LDH), low haptoglobin, indirect hyperbilirubinemia, and the presence of schistocytes on a peripheral blood smear [8]. The direct antiglobulin test is usually negative, except in cases associated with autoimmune disorders such as systemic lupus erythematosus. Coagulation parameters, including fibrinogen levels, are generally normal, which helps distinguish iTTP from disseminated intravascular coagulation. Mild renal impairment (serum creatinine $\leq 200 \mu\text{mol/L}$ [2.26 mg/dL]) is characteristic, although normal renal function may also be seen. Conversely, severe renal dysfunction suggests alternative diagnoses, such as HUS [8].

Because ADAMTS13 activity testing is not widely available in most centers and results may take several days, clinical prediction tools have been developed to support initial management decisions [2,8]. Both the French score [11] and the PLASMIC score [12] are highly predictive of severe ADAMTS13 deficiency (Table 1). In the French score, one point is assigned for each of the following: platelet count $\leq 30,000/\text{mm}^3$, serum creatinine $\leq 200 \mu\text{mol/L}$ (2.26 mg/dL), and the presence of detectable antinuclear antibodies. When at least one criterion is met, the positive predictive value for an iTTP diagnosis is approximately 85%, whereas the negative predictive value is 93.3% [11].

The PLASMIC score incorporates additional parameters and categorizes patients into low-, intermediate-, and high-risk groups [12,13]. High-risk patients (score 6–7) have a

greater than 90% likelihood of severe ADAMTS13 deficiency. This scoring system includes platelet count $< 30 \times 10^9/L$, evidence of hemolysis, absence of active cancer, no history of solid organ or stem cell transplantation, mean corpuscular volume (MCV) < 90 fL, international normalized ratio < 1.5 , and serum creatinine < 2.0 mg/dL [12,13]. Beyond this scoring system, age is an important prognostic factor, as older age [14] and certain comorbidities (e.g., arterial hypertension, ischemic heart disease) are associated with poorer outcomes [15]. Severe cerebral involvement is also an independent predictor of early mortality: patients presenting with a reduced Glasgow Coma Scale (GCS) score had a ninefold higher mortality rate during follow-up compared with those with a normal GCS at presentation (20% vs. 2.2%, $p < 0.0001$) [16].

Early recognition of iTTP is critical because of its high mortality rate if untreated [2,8,12]. Clinical predictors of severe ADAMTS13 deficiency facilitate timely initiation of therapy while awaiting confirmatory test results [17]. A high index of suspicion should be maintained in patients who present with MAHA and severe thrombocytopenia without an alternative cause. Early initiation of plasma exchange, immunosuppressive therapy, and adjunctive treatments such as caplacizumab has markedly improved survival in a condition once considered universally fatal [18,19].

TREATMENT OF ITTP

Plasma exchange

Because fresh frozen plasma (FFP) contains substantial amounts of ADAMTS13, plasma therapy—either therapeutic plasma exchange (TPE) or plasma infusion—can restore ADAMTS13 activity. Appropriate TPE reduces iTTP mortality from more than 90% to less than 10% [20]. TPE is classified as a category I treatment with the highest grade of recommendation (1A) according to the guidelines of the American Society for Apheresis and the International Society on Thrombosis and Haemostasis (ISTH) [21,22]. Therefore, TPE should be initiated as soon as iTTP is suspected. If TPE is not immediately available, high-volume plasma infusions (25–30 mL/kg) should be administered, if tolerated [21,22].

The FFP volume per TPE session is typically 1.0–1.5 times the patient's circulating plasma volume, and the duration of TPE depends on the clinical response and patient condition. Daily TPE is generally recommended until the platelet

count exceeds $150 \times 10^9/L$ and LDH levels approach normal for two to three consecutive days [21]. Because residual schistocytes may persist after TPE cessation, assessing their presence after treatment initiation is unnecessary [20–23].

Marn Pernat et al. [24] reported their 11-year experience with TPE in TTP treatment. Fifty-six patients underwent TPE once or twice daily until platelet counts normalized, with an average of 19 ± 17 plasma exchanges per patient and an average treatment duration of 23 ± 17 days [24]. In a study involving 52 Korean patients, including 14 with iTTP, the median number of TPE sessions was five (range, 1–32), and the remission rate was 71.4% [25].

Because randomized controlled trials have not established optimal duration or tapering strategies for TPE, these approaches remain debated. A commonly applied tapering regimen involves three sessions per week during the first week, two sessions during the second week, and one session weekly thereafter [21]. However, a prospective observational study found that tapering TPE did not reduce the rate of exacerbation in iTTP patients [26].

Corticosteroids

Corticosteroids are commonly used in combination with TPE as adjunctive therapy for iTTP. Before the advent of TPE, various treatments were attempted, and steroids were employed empirically among available options. Following several case reports and case series demonstrating their efficacy in iTTP, systematic steroid use increased in the late 1970s and 1980s, despite the unclear underlying mechanism. One study evaluated steroids as both an adjunct to TPE and as monotherapy [27], reporting that 28% of patients (30 of 108) with mild symptoms and no major central nervous system involvement (except for headache) responded to steroid therapy alone, suggesting that initial corticosteroid treatment can be feasible.

Although TPE remains the mainstay of iTTP management, corticosteroids play a supportive role. In cases of TTP associated with autoimmune disorders, steroids may have a greater therapeutic effect than in idiopathic cases. However, strong evidence for their efficacy in iTTP remains limited due to the scarcity of well-designed studies [2].

No consensus exists regarding the optimal corticosteroid dose, adjustment, or tapering strategy in iTTP. High-dose corticosteroids—such as prednisone (1 mg/kg/day orally) or methylprednisolone (125 mg intravenously, two to four times daily)—are generally used as initial therapy. If plate-

let counts fail to increase within three to four days, higher doses can be considered. Steroids are typically continued until platelet recovery and discontinuation of TPE, followed by gradual tapering over approximately three weeks. The tapering schedule should be individualized based on platelet count, ADAMTS13 activity, and neurological symptoms [22]. In real-world Korean practice, based on consensus among our authors, the initial regimen generally consists of intravenous methylprednisolone at approximately 1 mg/kg/day. This approach allows for the early addition of rituximab in cases of suboptimal response or clinical deterioration, while also minimizing steroid-related adverse effects.

Although the direct mechanism by which corticosteroids reduce or inhibit anti-ADAMTS13 autoantibodies remains uncertain, their adjunctive use alongside TPE is appropriate for patients with iTTP without contraindications, given the autoimmune nature of the disease. Nevertheless, careful monitoring is necessary to prevent steroid-related complications.

Rituximab

Acute episode

Rituximab, a chimeric anti-CD20 monoclonal antibody, plays a pivotal role in the management of iTTP by targeting B cells that produce anti-ADAMTS13 autoantibodies. This immunomodulatory mechanism promotes the restoration of ADAMTS13 activity and directly addresses the underlying autoimmune pathophysiology of the disease [22,28].

Internationally, rituximab has been increasingly incorporated into first-line therapy for iTTP, in combination with TPE and corticosteroids [22,28]. Several studies have shown that early administration of rituximab (within three days) significantly shortens hospitalization and reduces relapse risk [28,29]. However, the ISTH guidelines classify the addition of rituximab to corticosteroids and TPE during the first acute episode as a conditional recommendation, based on low-certainty, nonrandomized evidence [22].

The standard dosing regimen for rituximab in iTTP is 375 mg/m² once weekly for four weeks [28]. Recent investigations have explored low-dose regimens (100 mg weekly) and subcutaneous formulations as cost-effective alternatives that appear to maintain comparable efficacy [30].

Despite its international endorsement, rituximab is not currently reimbursed for iTTP in Korea. Consequently, its use is largely restricted to patients with relapsed or refractory

disease, where off-label administration occurs primarily in tertiary care settings. This reimbursement limitation underscores the need for policy reform, as restricted access may delay optimal immunosuppressive management.

Future policy revisions should aim to incorporate rituximab into the standard therapeutic regimen for iTTP, considering its proven potential to reduce relapse rates, decrease TPE dependency, and improve long-term outcomes [28,29]. This unmet clinical need is particularly pronounced in Korea, where caplacizumab remains unavailable, further emphasizing the importance of timely immunosuppressive therapy with rituximab.

Preemptive (prophylactic) use in remission

The integration of rituximab into TPE-based regimens has markedly improved treatment outcomes in patients with iTTP. Nevertheless, relapse remains a significant clinical concern, occurring in up to 50% of cases [31,32]. Growing evidence indicates that persistently low or fluctuating ADAMTS13 activity during remission is associated with an increased risk of relapse [33].

To mitigate this risk, preemptive administration of rituximab has been investigated in patients exhibiting low ADAMTS13 activity during remission. A pivotal French study involving 92 patients who achieved clinical remission after iTTP treatment but demonstrated persistently low ADAMTS13 activity (< 10%) during remission [32] found that those receiving preemptive rituximab had a significantly reduced relapse rate compared with historical controls, with a median of 0 episodes per year (interquartile range, 0–1.32; $p < 0.001$) [32]. Furthermore, among patients with undetectable ADAMTS13 activity after the initial rituximab course, re-treatment was effective in six of ten cases [32].

Similarly, a retrospective study from the United Kingdom evaluated preemptive rituximab in 45 patients (76 treatment episodes) with ADAMTS13 activity $\leq 15\%$. In this cohort, 78.9% of patients achieved normalization of ADAMTS13 activity ($\geq 60\%$), and 92.1% demonstrated at least a partial response ($\geq 30\%$). These results indicate that preemptive rituximab can restore ADAMTS13 activity in most patients and is associated with a reduced relapse risk or a significant delay in relapse onset [34].

Taken together, these findings highlight the clinical value of preemptive rituximab therapy in lowering iTTP relapse rates and prolonging remission duration. However, most available evidence is derived from studies employing histori-

cal control groups. Consequently, prospective, randomized, large-scale trials are needed to confirm these findings and establish standardized protocols for the preemptive use of rituximab in iTTP.

Caplacizumab

Caplacizumab is a humanized, bivalent, single-variable-domain immunoglobulin fragment (nanobody) that targets the A1 domain of vWF [35], thereby preventing its interaction with the platelet glycoprotein Ib-IX-V receptor [36]. By inhibiting vWF-platelet binding, caplacizumab effectively reduces microvascular thrombosis, the principal pathogenic mechanism in iTTP [37]. Its clinical efficacy has been demonstrated in randomized controlled trials, including the phase 3 HERCULES [19] and phase 2 TITAN [38] studies.

In the phase 3 HERCULES trial, caplacizumab significantly shortened the time to platelet count normalization compared with placebo (median, 2.69 vs. 2.88 days; $p = 0.01$) and resulted in a 74% reduction in the incidence of a composite endpoint comprising TTP-related death, recurrence, or thromboembolic events [19]. Moreover, the trial reported a 67% reduction in TTP recurrence during the study period [19]. Patients treated with caplacizumab required fewer TPE sessions, had shorter hospital stays, and exhibited lower rates of refractory disease than those receiving standard therapy [19]. The most frequently observed adverse event was mucocutaneous bleeding, which occurred more often in the caplacizumab group (65% vs. 48%), though severe bleeding events were rare [19]. Notably, three deaths occurred in the placebo group during the trial, whereas only one death—occurring after completion of the treatment phase—was reported in the caplacizumab group [19]. Similarly, the phase 2 TITAN trial [38] demonstrated a 39% reduction in the median time to platelet count normalization, along with fewer exacerbations and a lower relapse incidence in the caplacizumab group compared with placebo.

The clinical utility of caplacizumab has been further supported by real-world evidence confirming its effectiveness in rapidly controlling the acute phase of iTTP. This benefit is achieved by reducing the need for TPE, minimizing exacerbations and relapses, and preventing microvascular thrombosis-related organ damage [18,39-41]. Furthermore, an integrated analysis of the HERCULES and TITAN trials indicated a reduction in mortality during follow-up [42], while data from the French national registry demonstrated a 10% absolute reduction in mortality risk among patients treated

with caplacizumab [18]. Despite these benefits, concerns persist regarding its potential impact on ADAMTS13 activity recovery and associated bleeding risks. Some reports suggest that caplacizumab may delay ADAMTS13 recovery, as shown in a UK study in which the median time to achieving ADAMTS13 activity > 30 IU/dL was prolonged in caplacizumab-treated patients [43]. In contrast, other investigations—including an analysis from the Spanish Thrombotic Thrombocytopenic Purpura Registry—found no significant difference in ADAMTS13 recovery time when adjusted for the lower number of TPE sessions among caplacizumab recipients [39]. These discrepancies underscore the need for additional prospective studies to elucidate the long-term effects of caplacizumab on ADAMTS13 restoration and overall iTTP prognosis.

A major limitation of caplacizumab therapy is its high cost. A cost-effectiveness analysis employing a Markov model estimated an incremental cost-effectiveness ratio (ICER) of \$1,482,260 per quality-adjusted life year, which far exceeds the commonly accepted willingness-to-pay threshold [44]. Sensitivity analyses revealed that the drug's cost exerted the greatest influence on its ICER, suggesting that price reductions could substantially improve its cost-effectiveness [44]. Moreover, alternative dosing approaches—such as ADAMTS13 activity-guided discontinuation and non-daily administration regimens—have been investigated to reduce overall treatment costs without compromising efficacy [45]. Evidence indicates that discontinuing caplacizumab once ADAMTS13 activity exceeds 10% may represent a feasible strategy to prevent overtreatment and unnecessary drug exposure.

Caplacizumab is not yet available in Korea. However, given its demonstrated efficacy in reducing iTTP-related morbidity and mortality, its introduction into Korean clinical practice would represent a significant advancement in iTTP management. Furthermore, if robust evidence supporting non-daily dosing emerges, consideration should be given not only to maintaining standard dosing protocols but also to implementing optimized, non-daily regimens to balance clinical effectiveness with cost efficiency. Future research should aim to refine dosing algorithms and assess long-term outcomes associated with caplacizumab therapy, particularly with respect to ADAMTS13 activity restoration and cost-effectiveness across diverse healthcare systems.

Management of refractory iTTP

Refractory iTTP is defined as the absence of a platelet count increase ($> 50 \times 10^9/L$) with persistently elevated LDH levels ($> 1.5 \times$ the upper limit of normal) after five sessions of TPE, or a subsequent platelet decline during ongoing TPE [3]. In managing refractory iTTP, while implementing intensive therapies such as 1.5 plasma volume TPE, twice-daily TPE, and high-dose methylprednisolone (10 mg/kg or 1 g for three days, followed by 2.5 mg/kg), it is crucial to evaluate other possible causes of thrombocytopenia, including infection, drug-induced thrombocytopenia, and disseminated intravascular coagulation [46].

If not previously administered, rituximab should be considered when available. The recommended rituximab regimen is 375 mg/m² once weekly for four weeks, with each dose administered after completion of a plasma exchange session. Premedication is recommended to reduce the risk of severe infusion-related reactions. Several case series have reported that rituximab use in refractory or relapsing TTP achieved clinical remission in 87–100% of patients, with a median platelet recovery time of 11–14 days following the initial dose [47,48]. An alternative anti-CD20 monoclonal antibody, such as obinutuzumab, may be considered for patients who are intolerant to rituximab [49].

Caplacizumab as salvage therapy for refractory iTTP may be less effective than when used as an upfront treatment, owing to disseminated microvascular thrombosis and the resultant organ damage typically observed in refractory cases [50]. Nevertheless, several case reports have described clinical benefit even when caplacizumab was introduced at a later stage [51,52].

Plasma cell-depleting therapies, such as daratumumab or bortezomib, may be considered for refractory iTTP that persists despite anti-CD20 therapy [53,54]. These agents target long-lived plasma cells that continue to produce anti-ADAMTS13 autoantibodies and have demonstrated potential clinical benefit.

For patients who remain refractory, alternative immunosuppressive treatments should be considered, including cyclophosphamide (500 mg infused over two hours, single dose), vincristine (2 mg administered slowly, single dose), cyclosporine (300 mg/day orally or 2–3 mg/kg/day intravenously in two divided doses), mycophenolate mofetil (500–1,000 mg twice daily), azathioprine (1–2 mg/kg/day), or splenectomy [50].

Although recombinant ADAMTS13 (rADAMTS13) is pri-

marily approved for cTTP, a recent first-in-human study demonstrated that rADAMTS13 may serve as an effective salvage therapy in refractory iTTP by neutralizing inhibitory autoantibodies and restoring ADAMTS13 activity [55].

Definition of outcomes and response assessment

Standardized definitions of response, exacerbation, remission, and relapse were updated by the International Working Group for TTP in 2021. These revised definitions distinguish clinical remission and clinical relapse (determined primarily by platelet count) from ADAMTS13 remission and ADAMTS13 relapse (determined by ADAMTS13 activity) [46] (Table 2).

As discussed in the previous section, TPE is guided by platelet count and LDH level, the latter serving as a marker of hemolysis [21]. Because LDH levels are influenced by age [56,57] and coexisting medical conditions, decisions based solely on LDH results should be made with caution. If age-specific reference intervals for LDH are unavailable and the patient's baseline value is unknown, other indirect indicators of hemolysis—such as indirect bilirubin, reticulocyte count, haptoglobin, or MCV—should be assessed when necessary to evaluate treatment response, as reflected in the French and PLASMIC scoring systems [7,11,12]. Routine documentation of peripheral blood schistocytes during TPE is not recommended under the guidelines of the American Society for Apheresis [21]. However, platelet counts obtained from automated hematology analyzers can be affected by the presence of fragmented red blood cells, such as schistocytes [58,59]. Therefore, morphologic evaluation of a peripheral blood smear to rule out schistocytosis or other interfering artifacts may provide supportive evidence for the accuracy of platelet measurements. ADAMTS13 activity and anti-ADAMTS13 antibody titers are typically measured at initial presentation and during remission to aid in diagnosis and relapse prediction [7,60,61]. Because TPE both replenishes ADAMTS13 and removes anti-ADAMTS13 antibodies, remission can occur even before normalization of ADAMTS13 activity [62,63].

Follow-up of patients with iTTP and ADAMTS13 activity monitoring in remission (long-term follow-up)

In some patients, treatment decisions related to remission may need to be initiated during the platelet recovery phase,

Table 2. Revised outcome definitions for iTTP

Category	Outcome	Definition
Response	Clinical response	Sustained platelet count $\geq 150 \times 10^9/L$ and LDH < 1.5 times ULN and no clinical evidence of new or progressive ischemic organ injury.
Exacerbation	Clinical exacerbation	After a clinical response and before a clinical remission, platelet count decreases to $< 150 \times 10^9/L$ (with other causes of thrombocytopenia excluded), with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping TPE or anti-VWF therapy.
Remission	Clinical remission	Sustained clinical response with either no TPE and no anti-VWF therapy for ≥ 30 d or with attainment of ADAMTS13 remission (partial or complete), whichever occurs first.
	Partial ADAMTS13 remission	ADAMTS13 activity $\geq 20\%$ to $< LLN$. ^{a,b)}
	Complete ADAMTS13 remission	ADAMTS13 activity $\geq LLN$.
Relapse	Clinical relapse	After a clinical remission, platelet count decreases to $< 150 \times 10^9/L$ (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury. A clinical relapse must be confirmed by documentation of severe ADAMTS13 deficiency.
	ADAMTS13 relapse	After an ADAMTS13 remission (partial or complete), the ADAMTS13 level decreases to $< 20\%$. ^{a,b)}

iTTP, immune thrombotic thrombocytopenic purpura; LDH, lactate dehydrogenase; ULN, upper limit of normal; TPE, therapeutic plasma exchange; VWF, von Willebrand factor; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; LLN, lower limit of normal.

^{a)}ADAMTS13 level of 20% was chosen as the threshold for defining partial ADAMTS13 remission and ADAMTS13 relapse based on limited evidence that an ADAMTS13 level at or above this threshold is protective against clinical relapse. However, the precise ADAMTS13 threshold that confers protection from relapse remains uncertain and warrants further investigation.

^{b)}Because there is biological variability in ADAMTS13 level, as well as variability in its laboratory measurement, it may be advisable to repeat the test for ADAMTS13 level to confirm an ADAMTS13 remission or ADAMTS13 relapse.

Adapted from Cuker et al. [46].

when the risk of thrombosis remains elevated. In this setting, the 2025 ISTH guidelines recommend prophylactic anticoagulation—preferably with low-molecular-weight heparin—for patients with iTTP who have recovered platelet counts ($> 50 \times 10^9/L$) and are at increased risk of venous thrombosis, such as those with a history of recurrent venous thromboembolism, active cancer, or recent surgery. For patients with major thrombotic complications, a multidisciplinary management approach involving hematologists, neurologists, and cardiologists is advised [50].

With timely and effective therapy, most patients with iTTP achieve favorable outcomes after the first episode, with an overall survival rate of approximately 90%. However, recurrence occurs in 20–50% of cases [60]. Relapse or exacerbation of iTTP should be treated using an approach similar to that applied during the initial episode, taking into account prior treatment response and disease severity. TPE and corticosteroids should be promptly reinitiated. Rituximab should be considered, particularly if it was not used in the initial

episode or if relapse occurs in association with declining ADAMTS13 activity. Caplacizumab may be considered in selected patients, although its therapeutic role in relapsed or salvage settings remains limited. Overall, management should be individualized based on clinical presentation, previous therapeutic exposures, and resource availability.

The most reliable biomarker for predicting relapse is ADAMTS13 activity [60]. In patients in clinical remission, regular monitoring of ADAMTS13 activity is recommended. The ISTH guidelines advise monthly monitoring during the first three months, followed by assessments every three months during the first year and every 6–12 months thereafter [50]. If ADAMTS13 activity falls below 10%, testing for inhibitor titers and considering preemptive rituximab therapy are recommended [50].

Even among patients who remain in remission without clinical relapse or a measurable decline in ADAMTS13 activity, several studies have demonstrated a higher prevalence of hypertension, cognitive impairment, and major depressive

disorder compared with the general population, as well as a significantly increased risk of early mortality. Furthermore, TTP survivors face a higher-than-average risk of major cardiovascular diseases, neurocognitive deficits, and autoimmune disorders [64]. Given these concerns, cardiovascular risk factors that may directly influence survival should be routinely assessed, and appropriate preventive or therapeutic interventions should be implemented to reduce disease burden and improve long-term quality of life.

cTTP

cTTP is a rare autosomal recessive TMA caused by severe deficiency of the ADAMTS13 protease resulting from biallelic mutations. Diagnosis is confirmed by ADAMTS13 activity < 10% in conjunction with biallelic pathogenic variants in the *ADAMTS13* gene. The clinical presentation is highly variable, ranging from neonatal hyperbilirubinemia to recurrent episodes of thrombocytopenia, hemolysis, and organ ischemia, often precipitated by infections, trauma, or pregnancy. Many patients also experience chronic, non-overt symptoms—such as fatigue and migraine—between acute events [3,6,65].

Historically, cTTP has been managed with plasma-based ADAMTS13 replacement administered either on demand or prophylactically. Although this approach reduces acute episodes and mitigates organ damage, it is limited by the need for frequent infusions, the risk of allergic reactions, and subtherapeutic peak enzyme activity that necessitates regular monitoring and repeated dosing. Despite these challenges, plasma-based prophylaxis has been associated with a reduced risk of overt thrombotic events and end-organ complications in registry-based studies [66,67]. Notably, the 2025 ISTH guidelines recommend prophylactic plasma infusions over a watch-and-wait approach for patients with cTTP in remission [50].

Recently, rADAMTS13 was introduced as a novel therapeutic option. In a phase 3 crossover trial, rADAMTS13 prophylaxis effectively prevented acute episodes during the treatment period, achieved higher and more sustained enzyme activity levels, and demonstrated a favorable safety profile. Compared with plasma, rADAMTS13 is less immunogenic and better tolerated, supporting its role as a first-line prophylactic therapy [55].

Based on current evidence, expert consensus is shifting

toward the use of regular rADAMTS13 infusions every one to two weeks for patients with cTTP, particularly during periods of physiological stress such as pregnancy. As the therapeutic landscape continues to evolve, ongoing studies are warranted to refine dosing schedules, evaluate the long-term effects of early intervention, and assess the feasibility of home-based or subcutaneous administration. Expanding global access to rADAMTS13 remains an important goal for improving outcomes in this rare but serious disorder [68].

CONCLUSIONS

This Korean expert consensus summarizes the current evidence and international guidelines for the diagnosis and management of TTP, integrating the collective experience and practical perspectives of domestic experts to promote more timely and effective patient care in Korea.

Despite significant recent advances, several challenges persist. In Korea, the routine clinical availability of anti-ADAMTS13 antibody testing remains limited, and rituximab continues to be used off-label for iTTP, creating reimbursement barriers that delay early immunosuppressive intervention. Furthermore, caplacizumab has not yet been introduced into clinical practice, despite its proven efficacy during the acute phase of iTTP. Overcoming these regulatory and financial barriers will be essential to harmonizing Korean clinical practice with international standards and improving long-term patient outcomes.

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