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Diagnostic and treatment guidelines for thrombotic thrombocytopenic purpura (TTP) 2017 in Japan

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Abstract Thrombotic thrombocytopenic purpura (TTP) can rapidly progress into a life-threatening condition, thus the importance of appropriate diagnosis and treatment cannot be overstated. Until recently, TTP has mainly been diagnosed by clinical findings such as thrombocytopenia and non-immune hemolytic anemia. In addition to these clinical findings, however, reduced activity of a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) below 10% has been accepted internationally as a diagnostic criterion for TTP. In the present guidelines, we have taken all of these criteria into consideration. TTP is classified as acquired if the patient is positive for anti-ADAMTS13 autoantibodies, and as congenital if *ADAMTS13* gene abnormalities are detected. Fresh-frozen plasma (FFP) transfusion is performed in patients with congenital TTP to supplement ADAMTS13. Plasma exchange therapy using FFP is conducted in patients with acquired TTP to supplement ADAMTS13 and remove anti-ADAMTS13 autoantibodies. To suppress autoantibody production, corticosteroid therapy may be administered in conjunction with plasma exchange. Recent reports show that the monoclonal anti-CD-20 antibody rituximab is effective in patients with refractory or relapsed TTP.

Keywords TTP · ADAMTS13 · TMA

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a serious condition that develops as a result of platelet aggregation and systemic microvascular thrombosis [1]. Along with hemolytic uremic syndrome (HUS), TTP is a typical example of a thrombotic microangiopathy (TMA). TTP is characterized as either acquired or congenital. Previously, due to the absence of specific diagnostic markers, TTP was diagnosed primarily on the basis of the classic pentad of five signs and symptoms: thrombocytopenia,

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hemolytic anemia, renal failure, fever, and neurologic deficits. However, recent studies demonstrated an association between pathogenesis and severely reduced activity of a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) [2, 3]. This enzyme specifically cleaves von Willebrand factor (VWF), a glycoprotein necessary for normal hemostasis. Consequently, reduced ADAMTS13 activity has been included in the diagnostic criteria for TTP [4]. Congenital TTP is attributable to *ADAMTS13* gene mutations [5, 6], whereas acquired TTP develops as a result of anti-ADAMTS13 autoantibody production [2, 3].

The present diagnostic and treatment guidelines represent the consensus of expert physicians who are members of the TTP group in the Blood Coagulation Abnormalities team in the Health, Labour, and Welfare Scientific Research Grant Project funded by the Japanese government. Given the rarity of this disease, the authors acknowledge the difficulty of reviewing large populations of TTP patients. Nonetheless, we seek to provide the best possible evidence-based description of this condition. In these guidelines, separate sections are devoted to acquired and congenital TTP, and treatment recommendations are sorted by different levels of evidence, following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (Table 1). Treatments for acquired TTP relate only to adult patients, and attention should be paid to pharmacotherapies for pediatric TTP patients due to the lack of clinical experience in this population. Patients whose ADAMTS13 activity is ≥10% fall outside the scope of these guidelines, because such patients do not meet the criteria for designated intractable/rare diseases made by Japanese Ministry of Health, Labour and Welfare (MHLW) (ADAMTS13 activity <10% for TTP). That said, a certain population of patients clinically diagnosed with TTP have

been confirmed to show ADAMTS13 activity above 10%. Further research must be done to better understand their pathology. As with TTP patients who meet the criteria of the present guidelines, a proportion of such patients should undergo plasma exchange and other appropriate treatment without delay.

Pathology

ADAMTS13 is the 13th member of the ADAMTS family of metalloproteases [7]. VWF, the substrate of ADAMTS13, is mainly produced in vascular endothelial cells and released into the plasma as unusually large multimers, which readily undergo ADAMTS13 proteolysis [1]. The platelet-binding affinity of VWF multimers is dependent on their molecular weight. Thus, unusually large VWF multimers are more likely to form platelet thrombi than normal VWF [8]. Platelet–VWF interaction and adhesion are facilitated by high shear stress [9], which develops in the presence of fast blood flow and in small vessels. In patients with TTP, endothelial unusually large VWF multimers secreted into the blood stream tend to remain uncleaved due to low ADAMTS13 activity. In microvessels, exposure to high fluid shear stress induces a conformational change in VWF, which leads to platelet adhesion and subsequent thrombosis. Platelet thrombosis in the microvasculature causes damage to the kidneys, brain, and other end organs.

ADAMTS13 test

Initially, ADAMTS13 proteolytic activity was measured using full-length VWF as a substrate [10, 11]. Because this method is time-consuming, recent assays employ shorter synthetic derivatives [12–14], yielding results in several hours. Results are commonly reported relative to local pooled normal plasmas that are arbitrarily assigned values in units or percentages (1 U/mL or 100% is equivalent to the pooled normal plasma concentration of ADAMTS13).

Two types of anti-ADAMTS13 autoantibodies are recognized: neutralizing and non-neutralizing [15]. The former inhibits the protease in vitro (inhibitor), whereas the latter binds to, but does not suppress it. The majority of anti-ADAMTS13 autoantibodies are inhibitory immunoglobulin G (IgG), although a certain proportion of them are IgA or IgM [16]. In routine clinical practice, it is common to perform assays for only inhibitory ADAMTS13 autoantibodies, and non-neutralizing antibodies are measured largely for research purposes. One Bethesda unit (BU) is defined on the basis of 50% inhibition of ADAMTS13 activity when the test plasma is mixed with an equal amount of normal plasma [17]. The majority of

Table 1 Levels of recommendations based on the GRADE system

Strength of recommendations

1. Strong
   Benefits clearly outweigh risks and burden (or vice versa) in most patients
2. Weak
   Benefits are closely balanced with risks and burden

Quality of supporting evidence

A. Evidence established from multiple RCTs or very strong evidence from observational studies

B. Limited evidence from RCTs or strong evidence from observational studies

C. Evidence from RCTs with serious flaws or weak or indirect evidence from observational studies

GRADE Grading of Recommendations Assessment, Development and Evaluation, *RCT* randomized controlled trial

patients with acquired TTP have demonstrable levels of inhibitors [18, 19]. However, low inhibitor titers <1 BU/mL do not constitute convincing evidence for the diagnosis of acquired TTP. As described below, patients who are negative for ADAMTS13 inhibitors may nonetheless have acquired TTP involving autoantibody-mediated ADAMTS13 deficiency. Such patients have non-neutralizing autoantibodies, the presence of which is implicated by their clinical manifestations.

As of the end of March 2017, laboratory tests for ADAMTS13 activity and inhibitory autoantibodies are not subject to reimbursement in Japan.

Acquired TTP

Historical background

In 1924, the American physician Eli Moschcowitz documented the first presumed case of acquired TTP [20], and a series of similar cases without clear etiology were reported thereafter. In 1966, Amorosi and Ultmann described five common signs and symptoms [21], which are referred to as the classic TTP pentad. Among them, the diagnostic importance of thrombocytopenia and hemolytic anemia have gained increasing attention, and these conditions underscore the utility of plasma exchange [22]. Singer and colleagues were the first to use the term TTP, in a 1947 publication [23].

Whereas the clinical benefit of plasma exchange for treating TTP was demonstrated in 1991, its pathogenetic mechanism remained unknown. In the early 1980s, findings of unusually large VWF multimers in the plasma of TTP patients [24] and VWF-rich platelet thrombi at autopsy [25] suggested the involvement of VWF. In 1996, the assay method for VWF protease (ADAMTS13) activity was established [10, 11], and patients with TTP were reported in 1998 to show severely reduced ADAMTS13 activity [2, 3]. However, given that the diagnosis of acquired TTP is not necessarily associated with a marked reduction in ADAMTS13 activity [26–28], ADAMTS13 deficiency and clinical manifestations remained distinct diagnostic criteria. Physicians have debated the diagnostic threshold for ADAMTS13 activity reduction. There is growing international consensus on the use of activity levels <10% to support the diagnosis of TTP [29].

Definition

This condition is caused by systemic microvascular aggregation of platelets as a result of autoantibody-mediated severe ADAMTS13 deficiency.

Epidemiology

Overseas, the annual incidence rate of clinically diagnosed TTP has been estimated at 4–11 per million population [30, 31]. The incidence based on ADAMTS13 measurement is unknown. One group of researchers reported an incidence of 1.74 per million population using a diagnostic criterion of ADAMTS13 activity <5% [30]. In overseas studies of TTP based on ADAMTS13 activity, the median age at onset ranged from 36 to 51 years, with the proportion of females ranging from 65 to 100% [18, 27, 32, 33]. In a large study of Japanese patients with ADAMTS13-deficient TTP (ADAMTS13 activity <5%), median age at onset was 54 years, with a female proportion of 55% [19].

Diagnostic algorithm

If a patient presents with reduced platelet count and hemolytic anemia of unknown cause, the clinician should measure ADAMTS13 activity (Fig. 1). If the activity level is <10%, the patient is diagnosed with TTP. If the patient is positive for anti-ADAMTS13 autoantibodies, the patient is diagnosed with acquired TTP. Clinicians should be aware that patients may present with anti-ADAMTS13 autoantibodies even if they are negative for inhibitory autoantibodies. If the patient has no underlying disorders, they are diagnosed with primary acquired TTP. If anti-ADAMTS13 autoantibodies are produced secondary to systemic lupus erythematosus or other autoimmune diseases, or in response to ticlopidine or similar drugs, the diagnosis is secondary acquired TTP.

General laboratory thresholds related to the classic TTP pentad

Thrombocytopenia The general upper limit for platelet count is 100,000/μL for the diagnosis of thrombocytopenia. Most patients with TTP have platelet counts in the range of 10,000–30,000/μL. The median platelet count in a cohort of Japanese patients with TTP was 10,000/μL [19].

Hemolytic anemia Patients with acquired TTP exhibit microangiopathic hemolytic anemia, characterized by mechanical damage to red blood cells. Hemoglobin levels are typically in the range of 8–10 g/dL in overseas patients with TTP [34], whereas the median value in Japanese TTP patients has been reported as 7.3 g/dL [19]. The diagnosis of hemolytic anemia is made based on the following: the presence of schistocytes; increased levels of indirect bilirubin, lactate dehydrogenase, and reticulocytes; significantly decreased levels of haptoglobin; and negative
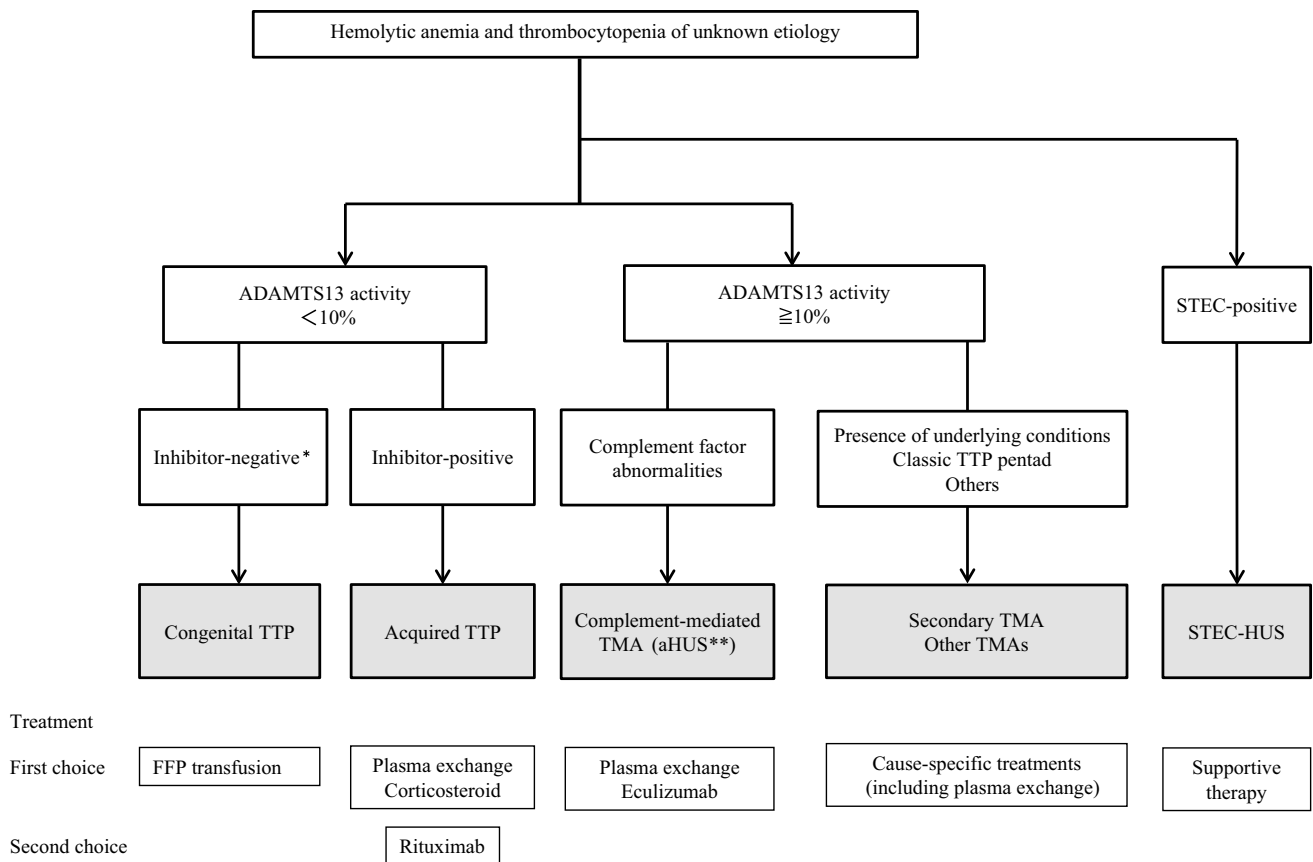
Fig. 1 Diagnostic and treatment algorithm for TMA. (*Asterisk*) The population of patients with acquired TTP includes a group of patients who are negative for ADAMTS13 inhibitors but positive for anti-ADAMTS13 antibodies. (*Double asterisks*) The term of atypical HUS (aHUS) is sometimes employed conventionally in health insurance and other documentation. *TMA* thrombotic microangiopathy, *TTP* thrombotic thrombocytopenic purpura, *ADAMTS13* a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13, *aHUS* atypical hemolytic uremic syndrome, *FFP* fresh frozen plasma, *STEC* Shiga toxin-producing *Escherichia coli*

direct Coombs test. Peripheral smears showing schistocyte percentage >1% in the absence of additional severe erythrocyte shape abnormalities are recommended as a robust indication for the diagnosis of TMA [35]. However, clinicians should be careful in regarding schistocytes as the hallmark of the disease, as the quantification of morphologic changes of blood cells is technically challenging and schistocytes may not always be present in the blood samples collected from patients with TTP.

Renal impairment Renal impairment may present as mild changes involving occult blood or positive urinary protein alone, while more severe cases may involve elevated serum creatinine levels. In most cases, the serum creatinine levels are <2 mg/dL [19]. Severe acute renal dysfunction that requires immediate hemodialysis is suggestive of HUS.

Fever Patients with TTP may present with a mild (37–39 °C) or high fever (>39 °C). Fever is documented in approximately 30% [32, 33] to 72% [19] of patients with TTP.

Fluctuating neurologic conditions Patients with TTP may develop a variety of neurologic conditions, ranging from mild headache to more severe manifestations involving delirium, confusion, personality change, decreased level of consciousness, quadriplegia, convulsions, etc. Neurologic manifestations usually fluctuate in severity and location, and often improve dramatically following plasma exchange. Neurologic involvement was reported in 79% of Japanese patients [19], and several overseas studies reported a rate of approximately 50% [18, 27].

Differential diagnosis

The diagnostic criterion based on ADAMTS13 activity provides a clear guidance for differentiating several common disorders from TTP, as described below. TMAs are

Table 2 Etiology-based subclassifications and clinical diagnoses of TMA

Etiology-based subclassification	Etiology	Underlying cause	Clinical diagnosis	Important clinical findings
ADAMTS13-deficient TMA	Severe decrease in ADAMTS13 activity	ADAMTS13 gene abnormality	Congenital TTP (Upshaw-Schulman syndrome)	ADAMTS13 gene abnormality
		Anti-ADAMTS13 autoantibodies	Acquired TTP	Severe decrease in ADAMTS13 activity and the presence of anti-ADAMTS13 autoantibodies
Infection-induced TMA	Infection	STEC (e.g., Escherichia coli O157)	STEC-HUS	STEC infection established by blood or stool culture
		Neuramidase-secreting Streptococcus pneumoniae	Pneumococcal-associated HUS	Proven pneumococcal infection
Complement-mediated TMA	Complement abnormality	Hereditary complement abnormalities (e.g., factors B, H, and I, C3, and membrane cofactor protein) Anti-factor H antibodies	Atypical HUS	Genetic complement factor abnormalities Low C3 and normal C4 levels (not necessarily observed in all patients with atypical HUS) Proven presence of anti-factor H antibodies
Coagulation-mediated TMA	Coagulation abnormality	Mutations in diacylglycerol kinase ε and thrombomodulin genes	Atypical HUS (possibly)	Proven genetic mutations
Secondary TMA	Unknown	Autoimmune diseases	Connective tissue disease-associated TMA, etc.	SLE, scleroderma, or other connective tissue disorders
		Hematopoietic stem cell transplant	Hematopoietic stem cell transplantation-associated TMA	Unresponsive to platelet transfusion Hemolysis (accompanied with, e.g., low haptoglobin levels)
		Organ transplant (e.g., kidney, liver)	Post-organ transplant TMA	Thrombocytopenia of unknown etiology and hemolysis (accompanied with, e.g., low haptoglobin levels)
		Malignant tumors	Tumor-associated TMA	Frequently diagnosed in patients with malignant lymphomas, stomach cancer, and pancreatic cancer
		Pregnancy	Pregnancy-associated TMA, HELLP syndrome	HELLP syndrome typically develops at 30 or more weeks of gestation in combination with hypertension
		Drugs (e.g., mitomycin)	Drug-induced TMA	Medication prescription
Other TMAs	Unknown	Other	TTP-like disorders or similar	Classic TTP pentad

TMA thrombotic microangiopathy, TTP thrombotic thrombocytopenic purpura, HUS hemolytic uremic syndrome, STEC Shiga toxin-producing Escherichia coli, C3 complement component 3, C4 complement component 4, SLE systemic lupus erythematosus, HELLP syndrome hemolysis, elevated liver enzymes, and low platelet count syndrome

subclassified by etiology. These etiology-based subclassifications correspond to clinical diagnoses, as shown in Table 2.

Disseminated intravascular coagulation

In patients with TTP, prothrombin time (PT) and activated partial thromboplastin time (APTT) are normal, fibrinogen and antithrombin levels typically remain in the normal range, and fibrin/fibrinogen degradation products (FDP) and D-dimer levels are mildly elevated. In contrast, disseminated intravascular coagulation (DIC) is usually characterized by fibrin thrombi, prolonged PT and APTT times, and reduced levels of fibrinogen.

Hemolytic uremic syndrome

HUS induced by Shiga toxin-producing *Escherichia coli* (STEC) strains, such as *E. coli* O157, can be diagnosed using (a) stool culture, enzyme immunoassay (EIA), and other methods for detecting STEC, or (b) methods for detecting anti-lipopolysaccharide (LPS) IgM antibodies. Formerly, cases of HUS unrelated to STEC infection were referred to as atypical HUS (aHUS). More recently, the term aHUS has been used to refer only to HUS involving complement abnormalities, such as complement factor H, component 3 (C3), and other elements [36], and is classified etiologically as a complement-mediated TMA.

HELLP syndrome

HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome occurs in connection with pregnancy-induced hypertensive nephropathy or preeclampsia, and can lead to multiple organ failure. The diagnostic criteria proposed by Sibai et al. are commonly used [37], but these criteria are not helpful for discriminating between HELLP syndrome and TTP. Patients with severely reduced ADAMTS13 activity should be diagnosed with TTP.

Evans syndrome

Evans syndrome is defined as the combination of autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura (ITP). Patients with Evans syndrome demonstrate a positive direct Coombs test. Certain patients diagnosed with Evans syndrome are direct Coombs-negative, and this patient group may include those who should be diagnosed with TTP based on a severe decrease in ADAMTS13 activity.

Secondary thrombotic microangiopathy

TMAs are reported to develop secondary to the following: systemic lupus erythematosus, scleroderma, and other connective tissue diseases; transplantation of hematopoietic stem cells, kidneys, and other organs; and malignant diseases. Although the exact etiology of secondary TMA is unknown, many scientists believe that it is primarily attributable to endothelial cell injury.

Other thrombotic microangiopathies

Some patients who are clinically diagnosed with TMA in the absence of underlying conditions do not satisfy the TTP criterion of a severe decrease of ADAMTS13 activity to <10%. This group of patients includes those who were formerly diagnosed with TTP based on the classic pentad.

Treatments

Plasma exchange is the only scientifically established treatment modality for acquired TTP [22]. In light of a report indicating that longer delay in initiating plasma exchange is an independent predictor of treatment failure [38], the clinician should initiate plasma exchange as soon as possible if the patient is suspected of having acquired TTP. The clinician should implement plasma exchange before the ADAMTS13 assay report is ready, since final results may not be available for several days after the assay is ordered. The following describes current treatment recommendations, along with grades of the strength of the recommendation (Table 1).

Acute phase

a) Plasma exchange (grade of recommendation: 1A)

The physician should carry out plasma exchange with FFP once daily. The FFP volume is 1.0–1.5 times of the patient's circulating plasma volume, which can be estimated using the equation below. The effectiveness of plasma exchange is attributable to: (1) ADAMTS13 supplementation, (2) removal of ADAMTS13 inhibitors, and (3) elimination of unusually large VWF multimers unsusceptible to proteolytic cleavage [28]. Human serum albumin solutions are not recommended for replacement, because these do not supplement ADAMTS13. FFP infusion may be performed in emergency cases. An analysis of response and survival showed that plasma exchange is superior to plasma infusion in the treatment of TTP [22].

Circulating plasma volume (mL) = body weight (kg) × 70 (mL/kg) × (1 − hematocrit value [%]/100).

Plasma exchange The physician should perform plasma exchange with FFP (50–75 mL/kg) once daily. Ideally, plasma exchange should be performed daily until 2 days after the platelet count is normalized (≥150,000/μL), as recommended by the UK guideline group [34]. However, this may not be practical in Japan due to Japanese health insurance policy restrictions (i.e., ≤3 times/week for a maximum of 3 months). For this reason, the physician should perform plasma exchange once daily for the first 5 days, followed by administration once every other day. The physician should determine the plasma exchange schedule based on the time course of change in platelet count and ADAMTS13 test results. Critically ill TTP patients may require plasma exchange more frequently than the government-determined reimbursable upper limit of 12 times per month.

b) Corticosteroid therapy (grade of recommendation: 1B)

Corticosteroids are administered either as intravenous pulse therapy or high-dose oral therapy. Available data on the superiority of either modality are inconclusive [39]. Corticosteroids are expected to suppress autoantibody production. The physician should consider lower doses in patients who are elderly or who have diabetes mellitus or severe infections. Although corticosteroid use in patients with TTP is considered off-label under current Japanese health insurance standards, it is classified as a Grade-1 recommendation based on its popularity as a TTP treatment in routine clinical practice.

Pulse corticosteroid therapy (not covered by Japanese health insurance).

Methylprednisolone 1000 mg/day for 3 days.

After receiving plasma exchange, the patient is administered methylprednisolone 1000 mg once daily over approximately 2 h by drip infusion. After the corticosteroid is administered by drip infusion at 1000 mg/day for three consecutive days, the dose should be tapered. The dose reduction regimen should be made with reference to platelet count and ADAMTS13 test results. No evidence-based procedure has been established for corticosteroid dose reduction. If the physician wishes to extend methylprednisolone therapy for the treatment of neurologic symptoms, or under conditions of intensive care unit (ICU) management, the corticosteroid may be administered at 500, 250, and 125 mg/day for 2 days each in this order. The dosage regimen should then be switched to oral corticosteroids 30 mg/day, and subsequently tapered with reference to the descriptions below. If the physician decides to switch to oral therapy after the first 3 days of drip infusion, the physician should orally administer predonisolone 0.5–1.0 mg/kg/day and taper the dose based on the following descriptions:

High-dose oral corticosteroid therapy (not covered by Japanese health insurance).

Prednisolone 1 mg/kg/day.

The physician tapers the prednisolone dose with reference to the platelet count and ADAMTS13 test results. The initial dose (1 mg/kg/day) is maintained for 2 weeks, followed by a rapid reduction to 0.5 mg/kg/day. The physician should further reduce the dose to the range of approximately 2.5–5.0 mg/week, taking note of the platelet count and ADAMTS13 test results.

c) Antiplatelet drugs (grade of recommendation: 2B)

Aspirin may be administered when the platelet count recovers to >50,000/μL. However, its impact on preventing TTP relapse is unsubstantiated.

Antiplatelet pharmacotherapy (not covered by Japanese health insurance).

Oral aspirin may be administered at a dose range of 81–100 mg once daily in the morning until the termination of corticosteroid use.

d) Other treatments

Patients without cardiac disorders may undergo red blood cell transfusion if hemoglobin levels decrease to <7.0 g/dL [34, 40]. In patients with cardiac disorders, hemoglobin levels <8.0 g/dL may suggest the need for red blood cell transfusion (grade of recommendation: 1A) [41]. Platelet transfusion may be indicated for patients with life-threatening bleeding. Prophylactic platelet transfusion in other situations, however, is contraindicated, as it may aggravate thrombosis (grade of recommendation: 1B) [34, 42, 43].

In patients manifesting TTP secondary to the use of a specific drug, the drug should be immediately discontinued. If the patient has an underlying condition, only drugs used to treat the condition should be continued. The physician conducts plasma exchange in patients with secondary TTP in a manner similar to those with primary TTP, as their ADAMTS13 activity levels may be severely lowered.

Patients with refractory TTP and those with early relapse

If the platelet count does not increase to 50,000/μL after five plasma exchange sessions, or if the platelet count decreases to <50,000/μL after initially recovering to >150,000/μL, the physician should consider rituximab in combination with plasma exchange (grade of recommendation: 1B) [44]. The physician should preferably

order both an ADAMTS13 activity assay and an inhibitor screen, as repeated plasma exchange sessions may elevate ADAMTS13 inhibitor titers [45]. Patients with a boosted inhibitor titer are often unresponsive to plasma exchange alone, thus necessitating combined use of rituximab. Rituximab takes 10–14 days to demonstrate a clinical impact, and plasma exchange should be conducted in the interim.

a) Rituximab (grade of recommendation: 1B) (not covered by Japanese health insurance)

Rituximab, an anti-CD20 monoclonal antibody, suppresses ADAMTS13 inhibitor production by depleting B lymphocytes. Although rituximab therapy for the treatment of TTP is not covered by Japanese health insurance, it is classified as Grade 1, as it is widely administered in clinical practice for treating patients with refractory TTP [44, 46, 47].

Rituximab therapy.

Rituximab 375 mg/m^2.

Rituximab is administered at increasing infusion rates using an infusion pump. It is administered after plasma exchange where appropriate.

The recommended rituximab therapy regimen is once weekly for four doses.

In addition to rituximab, the following therapies are typically available, but not always effective, for treating refractory or recurrent cases:

b) Cyclophosphamide (grade of recommendation: 2B) (not covered by Japanese health insurance) [48]

Cyclophosphamide 500 mg/body.

Cyclophosphamide is administered once daily over 2 h. Typically, the cyclophosphamide regimen is restricted to a single dose, as multiple doses may cause bone marrow suppression.

c) Vincristine (grade of recommendation: 2B) (not covered by Japanese health insurance) [49]

Vincristine 1 mg/body is administered intravenously once daily at a slow rate of infusion. The vincristine regimen is usually restricted to a single dose, as multiple doses may cause neurotoxicity and bone marrow suppression.

d) Cyclosporine (grade of recommendation: 2B) (not covered by Japanese health insurance) [50]

Oral cyclosporine 4 mg/kg/day is administered in two divided doses. Blood levels of cyclosporine should be monitored to maintain a trough level of approximately 100–200 ng/mL.

e) Other treatments (not covered by Japanese health insurance)

Formerly, splenectomy (grade of recommendation: 2C) [51] and high-dose immunoglobulin (grade of recommendation: 2C) [52] were frequently administered to treat patients with refractory or recurrent TTP. These treatments have been superseded by rituximab therapy.

Remission period

After the patient has achieved full remission, the physician should discontinue corticosteroids at the earliest opportunity, based on ADAMTS13 activity and inhibitor titer measurements. No effective prophylactic treatments are recommended for patients in remission. To minimize the risk of relapse, patients should visit the physician regularly during the first several years after achieving remission and undergo monitoring of the platelet count and ADAMTS13 activity. In patients in remission with normal platelet counts, ADAMTS13 activity may be severely reduced and ADAMTS13 inhibitors may be present [16, 53]. Patients whose ADAMTS13 activity is significantly reduced or who are positive for ADAMTS13 inhibitors are at high risk of relapse [16, 53].

Classification by severity

Table 3 summarizes the TTP severity classification scheme used in designated intractable/rare diseases made by Japanese MHLW for a medical expense support system. If the patient's condition meets one or more of these eight criteria, the condition is classified as moderate or

Table 3 Acquired TTP severity classification scheme

1. ADAMTS13 inhibitor titer ≥2 BU/mL
2. Renal failure
3. Neurologic dysfunction
4. Cardiac manifestations (elevated troponin levels, abnormal ECG findings, etc.)
5. Gastrointestinal symptoms (e.g., abdominal pain)
6. Deep vessel hemorrhage or thrombosis
7. Treatment resistance
8. Recurrence
Criteria and evaluation
Add 1 point for each "yes" response (0 points for "no")
Severe: ≥3
Moderate: 1–2
Mild: 0

severe, and the patient is eligible for the designated intractable/rare disease program.

Treatment outcome

TTP was formerly associated with a poor prognosis, with a mortality rate higher than 90% in untreated patients [21]. The introduction of plasma exchange, however, has elevated the survival rate to approximately 80% [18, 19, 22, 27, 32]. High levels of serum creatinine and ADAMTS13 inhibitor titers of two or more BU/mL are poor prognostic factors for patients with ADAMTS13 activities <10% [18]. Patients with acute TTP are at risk of cardiovascular death, and should undergo myocardial troponin I measurement [34].

Congenital TTP (Upshaw-Schulman syndrome)

Historical background

Early in the 1950s, neonatal cases characterized by severe jaundice and thrombocytopenia were documented [54]. In 1960, Schuman and colleagues [55] reported an 8-year-old girl who experienced repeated bleeding events associated with chronic thrombocytopenia from the neonatal period. One key clinical characteristic of this patient was that her platelet count remarkably improved following transfusion of small amounts of FFP. In 1978, Upshaw reported a similar case of a 28-year-old woman with chronic thrombocytopenia who also responded well to FFP transfusion [56]. These conditions were referred to as USS [57], and low blood fibronectin levels were associated with its etiology, although this theory was later refuted. Thereafter, the term USS was abandoned in the Western medical community and superseded by "chronic-relapsing (CR) TTP" [24]. While the latter term gained lasting popularity, it obscured the fact that TTP can be differentiated into congenital and acquired types. In 1982, Moake et al. made the important discovery that unusually large VWF multimers appear in patients with remitted CR-TTP [24, 58]. In 1997, Furlan et al. reported that VWF-cleaving protease (CP) activity is severely reduced in patients with CR-TTP [58]. The VWF-CP was later identified as ADAMTS13. The CR-TTP patient cohorts in these studies included individuals with both congenital and acquired TTP. Furlan et al. reported that the parents of the two sibling patients in the study had essentially normal VWF-CP activity. In a study of three Japanese USS patients reported in July 2001 [59], Kinoshita et al. showed that the VWF-CP activities of the patients were undetectable, while those of their parents ranged from 5.6 to 60% of control values. The authors concluded that USS is inherited in an autosomal recessive fashion. Levy

et al. conducted genome-wide positional cloning in four pedigrees of individuals with congenital TTP, and reported in an article published in December 2001 that *ADAMTS13* was the responsible gene [5]. These findings led to the recognition that USS is a congenital form of TTP arising from *ADAMTS13* gene abnormalities, and thus the terms "USS" and "congenital TTP" are synonyms. Two simple assays for determining ADAMTS13 activity were recently developed in Japan [13, 14], and these have accelerated the diagnosis of USS patients. At present, approximately one-third of the USS patients identified worldwide are from Japan.

Definition

Congenital TTP is a hereditary disorder resulting from systemic microvascular aggregation of platelets, and is attributable to *ADAMTS13* gene mutations causing severe ADAMTS13 deficiency. Its inheritance is autosomal recessive.

Epidemiology

The prevalence rate of congenital TTP is unknown. The population of patients with congenital TTP is assumed to be much smaller than that of patients with acquired TTP [60]. One European registry-based study estimated that the prevalence was in the range of 0.5–4 per million population [61]. A group of Japanese researchers estimated that this disease develops in 1 out of 1.1 million population [62]. By the end of 2015, 59 patients with congenital TTP have been identified in Japan. Since this disease exhibits autosomal recessive inheritance, it should theoretically develop at equal rates in both sexes. However, the group of 59 patients documented in Japan consists of 24 males and 35 females. The larger number of female patients with congenital TTP may be attributable to the greater chance of detection during pregnancy.

Depending on the timing of onset, this disease can be subcategorized into two types [63]:

Early onset Typically, patients with early-onset congenital TTP have a history of replacement transfusion for the treatment of severe neonatal jaundice. After repeated thrombocytopenic episodes in association with influenza and other infections, patients are diagnosed with congenital TTP and receive periodic FFP transfusion during childhood.

Adult onset Patients are diagnosed with congenital TTP in adulthood after experiencing thrombocytopenia in association with pregnancy, influenza, or other infections. Some patients who experience the onset of TTP in adulthood may have been misdiagnosed with ITP due to childhood thrombocytopenic episodes. As patients with congenital TTP have mild hemolytic anemia, they may remain undetected and undiagnosed. In female patients

with congenital TTP, pregnancy will provide a unique opportunity for detecting TTP signs and symptoms [64]. One Japanese male patient was diagnosed with TTP for the first time at the age of 63 [65].

Diagnosis

Congenital TTP is suspected if the patient presents with thrombocytopenia and ADAMTS13 activity <10% in the absence of ADAMTS13 inhibitors. However, it is not always technically feasible to determine whether the patient is positive or negative for ADAMTS13 inhibitors. In certain situations, differentiation between congenital and acquired TTP can only be made after monitoring ADAMTS13 activity and testing the ADAMTS13 activity of their parents. *ADAMTS13* gene analysis is required for the definitive diagnosis of congenital TTP. Because asymptomatic parents of a patient with congenital TTP have heterozygous mutations, their ADAMTS13 activities often range from 30 to 50% [6, 66].

Congenital TTP should be differentiated from ITP unresponsive to common medical management, as well as from pregnancy-induced complement-mediated TMA and HELLP syndrome. The physician should note that although congenital TTP always involves severely decreased ADAMTS13 activity, it is not necessarily accompanied by thrombocytopenia.

ADAMTS13 gene analysis

Congenital TTP is an autosomal recessive disorder involving homozygous or compound heterozygous *ADAMTS13* gene mutations [5, 67]. Of 55 Japanese patients with genetically confirmed congenital TTP, 10 and 45 had homozygous and compound heterozygous *ADAMTS13* gene mutations, respectively.

Treatment

FFP transfusion regimens effective in patients with congenital TTP vary depending on their condition; some patients require chronic treatment with periodic FFP transfusions, while others require episodic FFP transfusions only when their condition worsens. The volume of FFP and the duration of transfusion should be determined by taking into consideration platelet count changes and occult blood scores.

Fresh frozen plasma transfusion (grade of recommendation: 1B).

The physician should administer FFP at a volume of 5–10 mL/kg once every 2–3 weeks. At the time of onset, the physician should transfuse FFP at a volume of 10 mL/kg and monitor the clinical impact. To minimize the risks

Table 4 Congenital TTP severity classification scheme

1. Severe	Patients undergoing maintenance dialysis and patients with sequelae of stroke or other thrombotic events
2. Moderate	Patients who require fresh frozen plasma transfusion either periodically or episodically
3. Mild	Patients under observation without treatment

of allergy/anaphylaxis, disease transmission, and other adverse reactions to FFP infusion at the time of onset, efforts should be made to collect FFP from the smallest possible number of donors.

Classification by severity

Table 4 presents the congenital TTP severity classification scheme used in designated intractable/rare diseases made by Japanese MHLW for a medical expense support system. All cases of congenital TTP are covered by this system, except for mild cases that require no medical treatment.

Treatment outcome

Appropriate diagnosis and treatment with FFP transfusion will generally achieve excellent results in patients with congenital TTP. In Japan, eight deaths were documented among 59 patients diagnosed with congenital TTP. Five of these died after the start of hemodialysis treatment. These cases suggest that preventing renal deterioration may improve outcomes. It has been suggested that when FFP administration leads to anti-ADAMTS13 alloantibody formation in patients with congenital TTP, the clinical effects of FFP will be compromised. Although no such cases have been reported to date in Japan, this possibility underscores the importance of performing regular ADAMTS13 inhibitor assays.

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