International Journal of Hematology (2023) 117:331–340
https://doi.org/10.1007/s12185-023-03552-8

PROGRESS IN HEMATOLOGY

Progress in pathophysiology and treatment of thrombocytopenia

Frontiers in pathophysiology and management of thrombotic thrombocytopenic purpura

Masayuki Kubo[1] · **Masanori Matsumoto**[1]

Received: 15 December 2022 / Revised: 25 January 2023 / Accepted: 25 January 2023 / Published online: 9 February 2023

Abstract

Thrombotic thrombocytopenic purpura (TTP) is a fatal disease in which platelet-rich microthrombi cause end-organ ischemia and damage. TTP is caused by markedly reduced ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity. Hereditary or congenital TTP (cTTP) is caused by *ADAMTS13* gene mutations. In acquired or immune TTP (iTTP), ADAMTS13 activity is reduced by anti-ADAMTS13 autoantibodies. TTP is characterized by thrombocytopenia, hemolytic anemia, fever, renal dysfunction, and neuropsychiatric symptoms. Therapeutic plasma exchange (TPE) and immunosuppressive therapy are the mainstays of treatment. As untreated TTP has a high mortality rate, immediate initiation of TPE is recommended when TTP is suspected. Conventionally, corticosteroids have been used for immunosuppressive therapy. Current drug therapies include rituximab, an anti-CD20 antibody that is effective in newly diagnosed cases and refractory cases, as well as for relapse prevention, and caplacizumab, an anti- von Willebrand factor (VWF) nanobody that inhibits the binding of platelets to VWF and prevents microthrombi formation. Recombinant human ADAMTS13 is a promising treatment for cTTP. Although these therapeutic advances have improved the outcomes of TTP, early diagnosis and prompt initiation of appropriate therapy are necessary to achieve these outcomes.

Keywords Thrombotic thrombocytopenic purpura · ADAMTS13 protein · Plasma exchange · Rituximab · Caplacizumab

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease caused by the formation of platelet-rich microthrombi in small arterioles throughout the body [1]. TTP and hemolytic uremic syndrome are the most common forms of thrombotic microangiopathy (TMA) [2, 3]. Currently, TTP is diagnosed when TMA is caused by markedly reduced ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity [4, 5]. Congenital TTP (cTTP) is caused by *ADAMTS13* gene mutations [6, 7], whereas immune TTP (iTTP) is caused by anti-ADAMTS13 autoantibodies [4, 5]. Thrombocytopenia, hemolytic anemia, renal dysfunction, fever, and neurological deficits are the classic characteristic pentad of TTP symptoms [8]. ADAMTS13 activity should be tested, especially in patients with unexplained thrombocytopenia and hemolytic anemia, and when the activity is markedly reduced (< 10%), a diagnosis of TTP can be confirmed [3, 9]. Recently, the pathophysiological analysis of TTP has progressed considerably, and drugs with new pharmacological mechanisms based on this pathophysiology are being developed and tested in clinical trials. This review aims to provide an overview of the advances in the pathophysiological analysis and treatment of TTP.

Physiological function of von Willebrand factor and ADAMTS13

Von Willebrand factor (VWF) and ADAMTS13 are implicated in the pathogenesis of TTP. A mature VWF subunit with 2050 amino acid residues comprises the following domains: D′-D3-A1-A2-A3-D4-C1-C2-C3-C4-C5-C6-CK [10]. VWF subunits polymerize by disulfide bonds to form large multimers. VWF is primarily produced by vascular

✉ Masanori Matsumoto
mmatsumo@naramed-u.ac.jp

[1] Department of Blood Transfusion Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

endothelial cells and stored in Weibel-Palade bodies as ultra-large VWF multimers (UL-VWFMs). UL-VWFMs, secreted into the bloodstream in response to vascular injury or activation of vascular endothelial cells [10], have a high platelet-binding affinity, which increases the risk of thrombus formation.

ADAMTS13 is a proteolytic enzyme primarily produced in hepatic stellate cells that specifically degrades VWF [11]. ADAMTS13 cleaves the Tyr1605-Met1606 bond in the VWF A2 domain. VWF is folded under conditions of low shear stress, such as in the aorta; however, it unfolds under conditions of high shear stress, such as in the arterioles, exposing the cleavage site to ADAMTS13 [12]. In healthy individuals, UL-VWFMs are cleaved by ADAMTS13 and thrombus formation is suppressed [13].

Pathophysiology of TTP

In patients with TTP, ADAMTS13 activity is significantly reduced due to *ADAMTS13* gene mutations (cTTP) and anti-ADAMTS13 autoantibodies (iTTP). Consequently, UL-VWFMs remain in the circulation without being cleaved, forming platelet-rich thrombi in microvessels under conditions of high shear stress [1]. Thrombi formation in the inflow vessels of organs such as the kidneys and brain result in end-organ ischemia and damage. In addition, mechanical hemolysis of erythrocytes that traverse vessels narrowed by thrombus results in the formation of schistocytes in the peripheral blood. Herein, the notable factors involved in the pathogenesis of TTP are discussed in detail.

Anti-ADAMTS13 autoantibodies

Anti-ADAMTS13 autoantibodies include inhibitory (antibodies that inhibit the proteolytic activity of ADAMTS13) and non-inhibitory antibodies. Non-inhibitory antibodies bind to ADAMTS13 and increase its circulatory clearance [14]. The association between anti-ADAMTS13 antibody titers and prognosis has been noted, with higher mortality rates in patients having high antibody titers and low ADAMTS13 antigen levels [15]. Anti-ADAMTS13 antibodies are primarily composed of immunoglobulin G (IgG), approximately 90% of which are of the IgG4 type [16, 17]. Autoantibodies of IgA and IgM types are found in approximately 10–20% of patients [16, 18]. Patients with high titers of anti-ADAMTS13 IgA antibodies have low platelet counts, which is associated with severity of disease [19].

Anti-ADAMTS13 antibodies are formed against all domains of ADAMTS13; however, autoantibodies against the cysteine-rich/spacer (CS) domain were found in approximately 70% of patients with iTTP [17, 20–22] (Fig. 1A). Five residues (Arg568, Phe592, Arg660, Tyr661, and Tyr665) in exocite 3 of the spacer domain were identified as the major epitopes [23–25]. Additionally, autoantibodies to the CUB1-2 domain were found in approximately 30–50% of patients [17, 22]. Epitope mapping using small fragments of ADAMTS13 revealed that autoantibodies to the CS domain alone were the most common in approximately 25% of patients [17, 22]. However, several patients had autoantibodies to multiple domains, with many having both anti-CS and anti-CUB1-2 antibodies [17, 22]. Future studies should explore the relationship between the profile of autoantibodies and the clinical manifestations of the disease.

Conformational changes of ADAMTS13

The conformational change of ADAMTS13 in iTTP has garnered considerable attention. Normally, the interaction between the spacer and CUB domains results in a closed ADAMTS13 conformation [26–28]. However, when the CUB domain binds to the D4-CK domain of VWF, ADAMTS13 is activated and changes to an open conformation [27, 28] (Fig. 1B). The five residues of the epitope for anti-ADAMTS13 antibodies in the aforementioned spacer domain are normally concealed by the interaction between the spacer and CUB domains; however, they become exposed when ADAMTS13 changes to an open conformation [26, 29].

Recently, an open ADAMTS13 conformation was found during the acute phase of iTTP, and autoantibodies were revealed to have mediated this conformational change [30–32]. Conversely, in most patients with iTTP in remission, a closed ADAMTS13 conformation was found. Furthermore, in remission, an open ADAMTS13 conformation appears prior to the reduction of its activity and can be a biomarker for subclinical iTTP [31]. Future studies can provide detailed insights on the role and mechanisms of ADAMTS13 conformational changes in the pathophysiology of iTTP.

Genetic background

The association of genetic factors with specific HLA alleles has recently been indicated in the development of iTTP, as with other autoimmune diseases. HLA-DRB1*11 [33–35] and HLA-DRB1*08:03 [36] have been noted as risk alleles in Caucasians and the Japanese, respectively. In vitro and in silico analyses revealed that both alleles present peptides in the CUB domain with only one amino acid shift (FINVAPHAR and LFINVAPHA) [36, 37].

Infections may be associated with the development of iTTP; CD4 + T cells may react with ADAMTS13-derived peptides (CUB2 domain) that are homologous to microbial peptides and are present at risk alleles, leading to the development of iTTP [38].

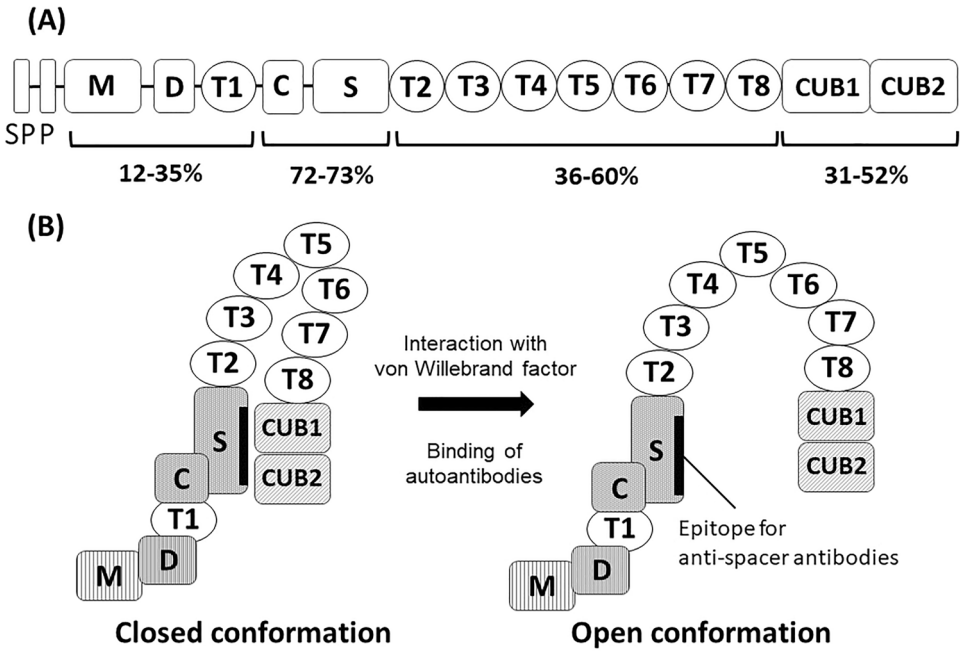

Fig. 1 Structure of ADAMTS13 protein. **A** Frequency of autoantibodies to each ADAMTS13 domain. ADAMTS13 comprises signal (SP), propeptide (P), metalloprotease (M), disintegrin (D), cysteine-rich (C), spacer (S), thrombospondin type 1 repeats (T1–8), and CUB domain. Anti-ADAMTS13 autoantibodies are formed against all domains of ADAMTS13. Most patients have autoantibodies only against the CS domain; however, many have autoantibodies against multiple domains [17, 20–22]. **B** Conformational changes in ADAMTS13. Normally, ADAMTS13 is in a closed conformation due to the interaction between the spacer and CUB domains [26–28]. However, ADAMTS13 changes to an open conformation by the interaction between the CUB and D4-CK (VWF) domains or by the binding of autoantibodies [27, 28, 32]

ADAMTS13 gene abnormalities

cTTP is an autosomal recessive disorder caused by *ADAMTS13* gene mutations. More than 200 mutations, distributed throughout the *ADAMTS13* gene, have been identified till date [39–41]. Missense mutations are the most common, followed by frameshift (deletions or insertions) and nonsense mutations [41]. There are regional differences in genotypes in patients with cTTP, and patients with a European ancestry have a higher frequency of p.R1060W and insertion c.4143_4144dupA [41, 42].

The clinical presentation of cTTP is classified into early- and adult-onset types [39]. Patients with the early-onset type may have received exchange transfusion for severe neonatal jaundice, and are diagnosed with cTTP in childhood when they present with repeated thrombocytopenia following common cold or other illnesses. Patients with the adult-onset type are diagnosed with cTTP, when they develop thrombocytopenia associated with pregnancy or infection. In a cohort study of 123 patients, the median age at which patients presented with their first symptoms was 4.5 years; however, it varied from birth to 69.8 years [41].

Several studies have reported on the factors that influence this diverse phenotype of cTTP. Residual ADAMTS13 activity is a known factor affecting the clinical course of the disease. ADAMTS13 activity < 3% is associated with early-onset type, more than one event per year, and the need for regular fresh frozen plasma (FFP) infusions [43]. Conversely, other studies have reported that residual ADAMTS13 activity is poorly correlated with age of onset and severity of cTTP [41], and the evidence is inconclusive. The aforementioned p.R1060W mutation has been identified more frequently in the adult-onset type, especially in women who developed an acute attack of TTP during their first pregnancy [44, 45]. However, patients with the identical genetic mutation may have different clinical presentation; thus, the relationship between genetic variants and phenotype remains unclear.

Diagnosis

Patients with thrombocytopenia and hemolytic anemia should be evaluated for TTP, and TTP is diagnosed when ADAMTS13 activity is < 10% [3, 9]. The International Society of Thrombosis and Haemostasis (ISTH) guidelines for TTP diagnosis state that an ADAMTS13 activity of 10–20% is equivocal and that clinical judgment to continue or discontinue treatment for TTP is required [9]. iTTP is diagnosed when the patient is positive for anti-ADAMTS13

autoantibodies. Furthermore, primary and secondary iTTP are diagnosed when the patient has no underlying diseases and has underlying diseases (such as an autoimmune disease or malignancy), respectively.

cTTP is suspected when ADAMTS13 activity is markedly reduced to < 10% and anti-ADAMTS13 autoantibody is negative. However, confirmation of the absence of autoantibodies is challenging. In a few cases, anti-ADAMTS13 autoantibodies were not detected at the time of initial diagnosis; however, autoantibodies were detected or ADAMTS13 activity was restored after treatment initiation, leading to the diagnosis of iTTP. If cTTP is suspected, ADAMTS13 activity should be evaluated in the parents and *ADAMTS13* gene analysis should be performed for a definitive diagnosis [3].

Treatment

Based on the pathophysiology, TTP treatment targets the following: (1) removal of UL-VWFMs; (2) removal and suppression of production of anti-ADAMTS13 autoantibodies; (3) inhibition of platelet/VWF thrombus; and (4) ADAMTS13 supplementation.

Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) is the standard treatment for iTTP, and its efficacy has been demonstrated in randomized controlled trials [46]. TPE has a favorable effect via the mechanisms of removal of UL-VWFMs and anti-ADAMTS13 autoantibodies and supplementation of ADAMTS13. It is recommended that TPE be performed once daily with FFP as replacement fluid until two days after the platelet count recovers to more than 150×10^9/L [47].

Untreated TTP is fatal; a delay in initiating TPE worsens the prognosis [48]. Therefore, TPE should be promptly initiated when iTTP is suspected. However, only a limited number of medical institutions are able to perform ADAMTS13-related testing in their in-house laboratories. In others, this testing is outsourced and hence, require several days to obtain results. According to the ISTH guidelines, the results of ADAMTS13 activity should ideally be available within 72 h, though a result within 7 days is acceptable [9]. The PLASMIC and French scores have been demonstrated as useful predictors of significant reduction in ADAMTS13 activity, if TPE must be initiated before the results of ADAMTS13 activity are available in patients with suspected TTP (Table1) [9, 49, 50]. In the high-risk group (scores 6–7) of the PLASMIC score, patients who received TPE had a significantly higher overall survival than those who did not receive TPE, while in the low/intermediate-risk group (scores 0–5), there was no difference in survival between patients with and without TPE [51].

Immunosuppressive therapy

Immunosuppressants are used to suppress the production of anti-ADAMTS13 autoantibodies in iTTP. Corticosteroids are commonly used, although clinical trials are yet to prove their efficacy. One month after completion of TPE, anti-ADAMTS13 autoantibodies were reported to be significantly suppressed and ADAMTS13 activity restored in the corticosteroids group than in the cyclosporine group [52].

Rituximab is a chimeric anti-CD20 monoclonal antibody. It suppresses anti-ADAMTS13 antibody production by depleting B lymphocytes via complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. The usual dosage is 375 mg/m^2 once a week for 4 weeks.

Table1 Predictive score for severe ADAMTS13 deficiency in suspected TTP [9]

Component	PLASMIC score [49]	French score [50]
Platelet count	$< 30 \times 10^9$/L (+1)	$< 30 \times 10^9$/L (+1)
Serum creatinine level	< 2.0 mg/dl (+1)	< 2.26 mg/dl (+1)
Hemolysis	+1	–
Indirect bilirubin > 2 mg/dl		
Or reticulocyte count > 2.5%		
Or undetectable haptoglobin		
No active cancer in previous year	+1	–
No history of solid organ or stem cell transplant	+1	–
INR < 1.5	+1	–
MCV < 90fL	+1	–
Likelihood of severe ADAMTS13 deficiency (ADAMTS13 activity < 10%)		
Low risk	0–4: 0–4%	0: 2%
Intermediate risk	5: 5–24%	1: 70%
High risk	6–7: 62–82%	2: 94%

INR international normalized ratio, *MCV* mean corpuscular value

When rituximab is used concurrently with TPE, it should ideally be administered after TPE, considering its clearance. Rituximab is reportedly effective in patients with refractory disease whose platelet counts do not recover despite conventional therapy and in those with early relapsed disease that worsens in a short period after clinical response. In these patients, rituximab can normalize platelet counts early and prevent short-term relapse after remission [53]. However, while rituximab prolongs the time to relapse, it may not reduce the long-term relapse rate [54, 55]; hence, careful long-term follow-up is required.

Additionally, rituximab is effective as initial therapy; it significantly shortens the time to remission and length of hospitalization, and reduces the frequency of TPE when used early after diagnosis and concurrently with TPE and corticosteroids [56]. Furthermore, rituximab is used to prevent relapse. Patients with significantly reduced ADAMTS13 activity in remission have a high relapse rate, and preemptive treatment with rituximab has been attempted for these patients [57, 58].

Ofatumumab and obinutuzumab, fully humanized second-generation anti-CD20 antibodies, have been reported to be effective and safe in patients with iTTP who were intolerant to rituximab due to adverse events such as drug hypersensitivity [59, 60].

Anti-tumor agents for multiple myeloma have been demonstrated to be effective for refractory, especially rituximab-resistant iTTP; these agents may possibly suppress antibody production by targeting plasma cells. Although limited to case reports, the efficacy of bortezomib, a proteasome inhibitor, and daratumumab, an anti-CD38 antibody agent, have been reported for rituximab-resistant iTTP [61, 62].

Anti-VWF therapy

Immunosuppressive therapy requires a certain period of time for the onset of its action, and fatal thrombosis cannot be avoided during this period; this has been indicated as a disadvantage of conventional iTTP therapy. Anti-VWF therapy is a possible preventive treatment for such thrombosis.

Caplacizumab is a bivalent humanized single-variable domain of heavy-chain antibody or nanobody that binds to the A1 domain of VWF, inhibits the adhesion of VWF to platelets, and thereby prevents thrombus formation. Its efficacy and safety have been demonstrated in two randomized controlled trials: phase II (TITAN study) and phase III (HERCULES trial) studies [63, 64]. In addition to TPE and immunosuppressive therapy, patients received either 10 mg of caplacizumab or placebo by intravenous infusion once before the first TPE, followed by subcutaneous infusion once daily until 30 days after TPE. The primary endpoint—the time to platelet count normalization—was significantly lesser in the caplacizumab group than in the placebo group. The key secondary endpoints—the composite endpoint of TTP-related mortality, recurrence, and thromboembolism—were significantly lower in the caplacizumab group than in the placebo group. A subsequent integrated analysis of the aforementioned studies revealed that caplacizumab reduced the mortality rate and refractoriness to treatment [65]. Mucocutaneous bleeding, such as epistaxis and gingival bleeding, was the most frequent adverse event in the caplacizumab group; however, it was mild in most patients.

Regarding the duration of use of caplacizumab, based on the results of clinical trials, the recovery of ADAMTS13 activity was considered an important indicator. In the phase II trial, early relapse was frequently observed in patients with persistently reduced ADAMTS13 activity at the time of discontinuation of caplacizumab. Therefore, in the phase III trial, such patients were allowed to continue caplacizumab for a maximum of 28 days beyond the initial 30 days, resulting in a reduction of early recurrence after discontinuation of the drug [64]. Caplacizumab was assumed to prevent end-organ ischemia and damage and death by inhibiting the formation of thrombi early in the course of the disease, thereby acting as a bridge until the onset of action of immunosuppressive therapy [66].

Caplacizumab was approved in Europe and the United States in 2018 and 2019, respectively, and has become the frontline treatment for iTTP in many countries. Post-marketing real-world data from several countries have been reported (Table 2) [67–70]. Nonetheless, owing to the high cost of the drug, its usage in all patients remains controversial [71]. Some studies have reported the cost-effectiveness of adding caplacizumab to conventional therapy [72]; however, further validation is needed.

ADAMTS13 supplementation therapy

Patients with cTTP are usually treated with FFP infusion to replenish ADAMTS13 [3, 73]. The frequency of FFP administration varies from regular prophylactic infusions in patients with repeated exacerbations to on-demand infusions only during exacerbations. However, FFP infusion may cause allergic reactions such as urticaria and post-transfusion infections. Recombinant human ADAMTS13 (rhADAMTS13) has recently been developed; in a Phase I trial for patients with cTTP, the use of rhADAMTS13 resulted in a dose-dependent increase of ADAMTS13 antigen levels and activity and a decrease in VWF multimer size [74]. Neither allergic reactions nor serious adverse events were observed, which indicated the safety of the product.

Regarding the use of rhADAMTS13 against iTTP, autoantibodies may possibly neutralize rhADAMTS13; however, it has been indicated that this activity may be restored by administering higher doses [75]. Furthermore,

Table 2 Real-world data on the efficacy and safety of caplacizumab for immune thrombotic thrombocytopenic purpura

	Völker et al. [67]	Coppo et al. [68]	Dutt et al. [69]	Pascual Izquierdo et al. [70]
Country	Germany	France	UK	Spain
Number of patients, *n*	60	90	85	77
Age, years	45.7 (22–83) mean (range)	45(34–57) median (IQR)	46 (3–82) mean (range)	47.1 ± 14, mean ± SD
Female, *n* (%)	42 (70%)	63 (70%)	56 (66%)	58 (75%)
Treatment				
TPE, *n* (%)	58 (96.7%)	90 (100%)	85 (100%)	77 (100%)
Corticosteroids, *n* (%)	59 (98.3%)	88 (98%)	84 (99%)	77 (100%)
Rituximab, *n* (%)	48 (80%)	90 (100%)	84 (99%)	65 (84%)
Data on caplacizumab				
Use of caplacizumab as a frontline therapy, *n* (%)	35 (58.3%)	90 (100%)	NR*	44 (57.1%)
Time to receive the first dose of caplacizumab, days	3 (0–27) after disease onset, median (range)	0 (0–4) after initiation of TPE, median (range)	2 (1–3) after initiation of TPE, median (IQR)	5 (2–11) after initiation of TPE, median (IQR)
Total duration of caplacizumab, days	34 (2–211) median (range)	33(29–38) median (range)	32(22–47) median (IQR)	35 (31–40) median (IQR)
Outcome data				
Time to normalization of platelet count after caplacizumab start, days	3 (1–13) median (range)	5 (4–6) median (IQR)	3 (2–4) median (IQR)	NR
TPE, days	9 (2–41) median (range)	5 (4–7) median (IQR)	7 (5–14) median (IQR)	(1) NR (2) 8.5 (6–12.5) median (IQR)
Hospitalization, days	18 (5–79) median (range)	13 (9–19) median (IQR)	12 (8–24) median (IQR)	(1) NR (2) 12 (9–15) median (IQR)
ICU stay, days	4 (0–46) median (range)	NR	4 (2–7)** median (IQR)	(1) NR (2) 2 (0–4) median (IQR)
Refractoriness, *n* (%)	19 (31.7%)	1 (1.1%)	NR	(1) 5/77 (6.5%) (2) 2/44 (4.5%)
Exacerbations, *n* (%)	2 (3.3%)	3 (3.4%)	2 (2%)	(1) 4/77 (5.2%) (2) 2/44 (4.5%)
Relapse, *n* (%)	2 (3.3%)	1 (1.1%)	3 (4%)	NR
Mortality, *n* (%)	1 (1.7%)	1 (1.1%)	5 (6%)	(1) 3/77 (3.9%) (2) 2/44 (4.5%)
Safety data				
Bleeding, *n* (%)	NR	30 (33%)	17 (20%)	16 (20%)
Major bleeding, *n* (%)	1 (1.7%)	2 (2.2%)	5 (5.9%)	2 (2.6%)
Remarks			*Seventy-four patients (87%) received caplacizumab within 1 week of starting TPE **Duration of intubation	Outcomes are described separately for the following: (1) patients treated with caplacizumab ($n=77$) and (2) patients treated with caplacizumab as initial therapy ($n=44$)

TPE therapeutic plasma exchange, *ICU* intensive care unit, *NR* not reported, *SD* standard deviation, *IQR* Interquartile range

ADAMTS13 mutant variants can resist autoantibodies by the replacement of amino acids [76] or insertion of N-glycans in the spacer domain [77] and its clinical application is expected in the near future.

Future prospects for TTP treatment

TPE has been the mainstay of iTTP treatment for many years, and survival rates of approximately 80% have been

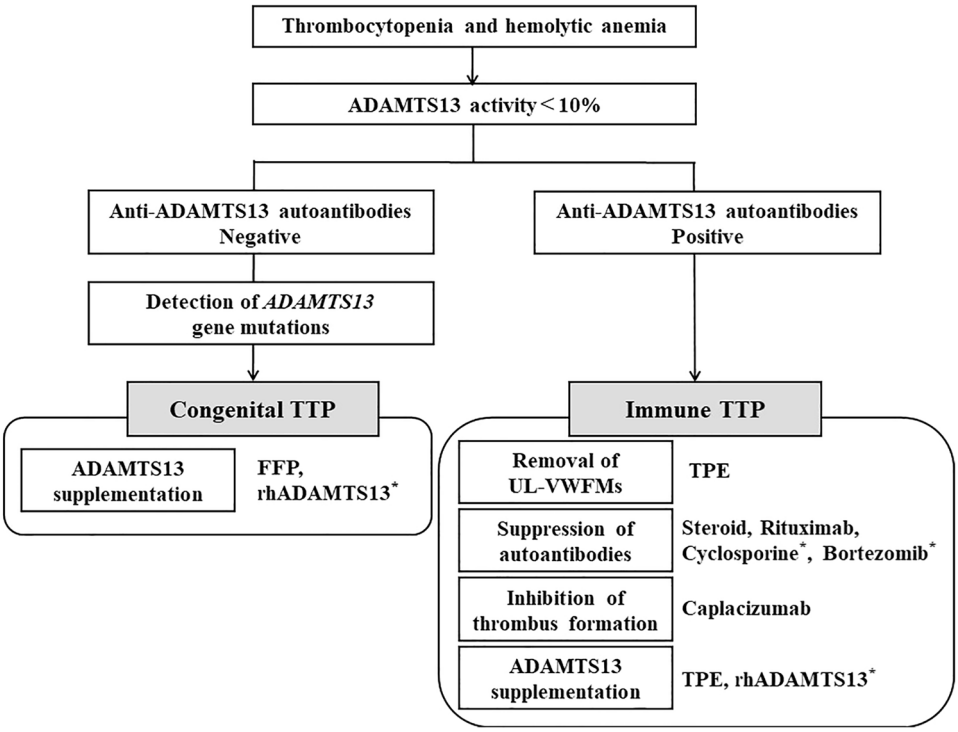

Fig. 2 Flowchart illustrating the diagnosis and treatment of thrombotic thrombocytopenic purpura. Patients with thrombocytopenia and hemolytic anemia are diagnosed with TTP when ADAMTS13 activity is < 10% [3, 9]. If anti-ADAMTS13 autoantibodies are positive, immune TTP is diagnosed. If anti-ADAMTS13 autoantibodies are negative, *ADAMTS13* gene analysis is performed. If gene mutations are detected, congenital TTP is diagnosed. Treatment of immune TTP targets the following: (1) removal of UL-VWFMs (TPE), (2) suppression of anti-ADAMTS13 autoantibodies (immunosuppressive therapy), (3) inhibition of thrombus formation (anti-VWF therapy), and (4) ADAMTS13 supplementation (TPE, rhADAMTS13). Congenital TTP is treated with ADAMTS13 supplementation (FFP, rhADAMTS13.) *Not approved for TTP in Japan. *TTP* thrombotic thrombocytopenic purpura, *UL-VWFMs* ultra-large von Willebrand factor multimers, *TPE* therapeutic plasma exchange, *FFP* fresh frozen plasma, *rhADAMTS13* recombinant human ADAMTS13

achieved post-implementation [78]. However, TPE has disadvantages such as procedural complications and allergy to human plasma [79]. Recently, with the advent of caplacizumab, the treatment of iTTP without TPE has been highlighted. A study reported that a patient with iTTP who refused TPE because of religious beliefs achieved remission with only caplacizumab and immunosuppressive therapy [80]. Another study from Germany and Austria reported that seven patients with iTTP were treated with only caplacizumab and immunosuppressive therapy and all had favorable outcomes. These findings indicate that TPE may be omitted in select cases [81]. In addition, rhADAMTS13 may be considered as a newer strategy in the treatment of iTTP without TPE. Future clinical trials should compare iTTP therapy with or without TPE.

In addition, long-term complications after remission remain a concern in iTTP. These include neuropsychological disturbances such as headaches, poor concentration, and memory impairment even after remission [82, 83]; a higher incidence of psychological conditions such as depression and post-traumatic stress disorder [82, 84]; and cardiovascular disease and renal dysfunction [85, 86], which might be attributed to end-organ damage caused by microthrombi during the acute phase of the disease. Caplacizumab may reduce long-term complications by inhibiting thrombus formation and rapidly ameliorating acute end-organ damage. Therefore, long-term follow-up is required for patients with TTP and patient data on neuropsychological and physical comorbidities should be prospectively collected.

Conclusion

Herein, we have reviewed the pathophysiological analysis and current therapeutic management approaches of TTP. The diagnosis and treatment of TTP are summarized in Fig. 2. The symptoms of TTP are diverse, and because of the emergent nature of the disease, patients may present to various departments other than hematology. Untreated TTP is fatal; however, recent advances in treatment, including novel therapeutic agents, have considerably improved the outcomes of patients who receive prompt and appropriate

treatment. Therefore, an early diagnosis and a multidisciplinary interdepartmental care approach are crucial to provide appropriate treatment.

Author contributions MK reviewed the articles on TTP and wrote the manuscript. MM reviewed and edited the manuscript.

Data availability statement Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of interest MM is an inventor of the ELISA used to assess ADAMTS13 activity and has received research funds from Chugai Pharmaceutical and lecture fees from Sanofi, Alexion Pharmaceuticals, and Takeda Pharmaceutical. MK has no conflicts of interest.

References

1. Sadler JE. Pathophysiology of thrombotic thrombocytopenic purpura. Blood. 2017;130:1181–8.
2. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371:654–66.
3. Matsumoto M, Fujimura Y, Wada H, Kokame K, Miyakawa Y, Ueda Y, et al. Diagnostic and treatment guidelines for thrombotic thrombocytopenic purpura (TTP) 2017 in Japan. Int J Hematol. 2017;106:3–15.
4. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med. 1998;339:1578–84.
5. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med. 1998;339:1585–94.
6. Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN, McGee BM, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 2001;413:488–94.
7. Kokame K, Matsumoto M, Soejima K, Yagi H, Ishizashi H, Funato M, et al. Mutations and common polymorphisms in *ADAMTS13* gene responsible for von Willebrand factor-cleaving protease activity. Proc Natl Acad Sci USA. 2002;99:11902–7.
8. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. Medicine. 1966;45:139–60.
9. Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, et al. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18:2486–95.
10. Lenting PJ, Christophe OD, Denis CV. Von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends. Blood. 2015;125:2019–28.
11. Uemura M, Tatsumi K, Matsumoto M, Fujimoto M, Matsuyama T, Ishikawa M, et al. Localization of ADAMTS13 to the stellate cells of human liver. Blood. 2005;106:922–4.
12. Schneider SW, Nuschele S, Wixforth A, Gorzelanny C, Alexander-Katz A, Netz RR, et al. Shear-induced unfolding triggers adhesion of von Willebrand factor fibers. Proc Natl Acad Sci U S A. 2007;104:7899–903.
13. Zhang X, Halvorsen K, Zhang CZ, Wong WP, Springer TA. Mechanoenzymatic cleavage of the ultralarge vascular protein von Willebrand factor. Science. 2009;324:1330–4.
14. Scheiflinger F, Knöbl P, Trattner B, Plaimauer B, Mohr G, Dockal M, et al. Nonneutralizing IgM and IgG antibodies to von Willebrand factor-cleaving protease (ADAMTS-13) in a patient with thrombotic thrombocytopenic purpura. Blood. 2003;102:3241–3.
15. Alwan F, Vendramin C, Vanhoorelbeke K, Langley K, McDonald V, Austin S, et al. Presenting ADAMTS13 antibody and antigen levels predict prognosis in immune-mediated thrombotic thrombocytopenic purpura. Blood. 2017;130:466–71.
16. Ferrari S, Mudde GC, Rieger M, Veyradier A, Kremer Hovinga JA, Scheiflinger F. IgG subclass distribution of anti-ADAMTS13 antibodies in patients with acquired thrombotic thrombocytopenic purpura. J Thromb Haemost. 2009;7:1703–10.
17. Sakai K, Matsumoto M, De Waele L, Dekimpe C, Hamada E, Kubo M, et al. ADAMTS13 conformation and immunoprofiles in Japanese patients with immune-mediated thrombotic thrombocytopenic purpura. Blood Adv. 2022;140:2790–1.
18. Rieger M, Mannucci PM, Kremer Hovinga JA, Herzog A, Gerstenbauer G, Konetschny C, et al. ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. Blood. 2005;106:1262–7.
19. Bettoni G, Palla R, Valsecchi C, Consonni D, Lotta LA, Trisolini SM, et al. ADAMTS-13 activity and autoantibodies classes and subclasses as prognostic predictors in acquired thrombotic thrombocytopenic purpura. J Thromb Haemost. 2012;10:1556–65.
20. Luken BM, Turenhout EA, Hulstein JJ, Van Mourik JA, Fijnheer R, Voorberg J. The spacer domain of ADAMTS13 contains a major binding site for antibodies in patients with thrombotic thrombocytopenic purpura. Thromb Haemost. 2005;93:267–74.
21. Zheng XL, Wu HM, Shang D, Falls E, Skipwith CG, Cataland SR, et al. Multiple domains of ADAMTS13 are targeted by autoantibodies against ADAMTS13 in patients with acquired idiopathic thrombotic thrombocytopenic purpura. Haematologica. 2010;95:1555–62.
22. Kangro K, Roose E, Joly BS, Sinkovits G, Falter T, von Auer C, et al. Anti-ADAMTS13 autoantibody profiling in patients with immune-mediated thrombotic thrombocytopenic purpura. Blood Adv. 2021;5:3427–35.
23. Klaus C, Plaimauer B, Studt JD, Dorner F, Lämmle B, Mannucci PM, et al. Epitope mapping of ADAMTS13 autoantibodies in acquired thrombotic thrombocytopenic purpura. Blood. 2004;103:4514–9.
24. Pos W, Sorvillo N, Fijnheer R, Feys HB, Kaijen PH, Vidarsson G, et al. Residues Arg568 and Phe592 contribute to an antigenic surface for anti-ADAMTS13 antibodies in the spacer domain. Haematologica. 2011;96:1670–7.
25. Pos W, Crawley JT, Fijnheer R, Voorberg J, Lane DA, Luken BM. An autoantibody epitope comprising residues R660, Y661, and Y665 in the ADAMTS13 spacer domain identifies a binding site for the A2 domain of VWF. Blood. 2010;115:1640–9.
26. South K, Luken BM, Crawley JT, Phillips R, Thomas M, Collins RF, et al. Conformational activation of ADAMTS13. Proc Natl Acad Sci USA. 2014;111:18578–83.
27. Muia J, Zhu J, Gupta G, Haberichter SL, Friedman KD, Feys HB, et al. Allosteric activation of ADAMTS13 by von Willebrand factor. Proc Natl Acad Sci USA. 2014;111:18584–9.
28. Deforche L, Roose E, Vandenbulcke A, Vandeputte N, Feys HB, Springer TA, et al. Linker regions and flexibility around the metalloprotease domain account for conformational activation of ADAMTS-13. J Thromb Haemost. 2015;13:2063–75.
29. Gao W, Anderson PJ, Sadler JE. Extensive contacts between ADAMTS13 exosites and von Willebrand factor domain A2 contribute to substrate specificity. Blood. 2008;112:1713–9.
30. Roose E, Schelpe AS, Joly BS, Peetermans M, Verhamme P, Voorberg J, et al. An open conformation of ADAMTS-13 is a hallmark of acute acquired thrombotic thrombocytopenic purpura. J Thromb Haemost. 2018;16:378–88.

31. Roose E, Schelpe AS, Tellier E, Sinkovits G, Joly BS, Dekimpe C, et al. Open ADAMTS13, induced by antibodies, is a biomarker for subclinical immune-mediated thrombotic thrombocytopenic purpura. Blood. 2020;136:353–61.
32. De Waele L, Curie A, Kangro K, Tellier E, Kaplanski G, Männik A, et al. Anti-cysteine/spacer antibodies that open ADAMTS13 are a common feature in iTTP. Blood Adv. 2021;5:4480–4.
33. Scully M, Brown J, Patel R, McDonald V, Brown CJ, Machin S. Human leukocyte antigen association in idiopathic thrombotic thrombocytopenic purpura: evidence for an immunogenetic link. J Thromb Haemost. 2010;8:257–62.
34. Coppo P, Busson M, Veyradier A, Wynckel A, Poullin P, Azoulay E, et al. HLA-DRB1*11: a strong risk factor for acquired severe ADAMTS13 deficiency-related idiopathic thrombotic thrombocytopenic purpura in Caucasians. J Thromb Haemost. 2010;8:856–9.
35. John ML, Hitzler W, Scharrer I. The role of human leukocyte antigens as predisposing and/or protective factors in patients with idiopathic thrombotic thrombocytopenic purpura. Ann Hematol. 2012;91:507–10.
36. Sakai K, Kuwana M, Tanaka H, Hosomichi K, Hasegawa A, Uyama H, et al. HLA loci predisposing to immune TTP in Japanese: potential role of the shared ADAMTS13 peptide bound to different HLA-DR. Blood. 2020;135:2413–9.
37. Sorvillo N, van Haren SD, Kaijen PH, ten Brinke A, Fijnheer R, Meijer AB, et al. Preferential HLA-DRB1*11-dependent presentation of CUB2-derived peptides by ADAMTS13-pulsed dendritic cells. Blood. 2013;121:3502–10.
38. Verbij FC, Fijnheer R, Voorberg J, Sorvillo N. Acquired TTP: ADAMTS13 meets the immune system. Blood Rev. 2014;28:227–34.
39. Fujimura Y, Matsumoto M, Isonishi A, Yagi H, Kokame K, Soejima K, et al. Natural history of Upshaw-Schulman syndrome based on *ADAMTS13* gene analysis in Japan. J Thromb Haemost. 2011;9(Suppl 1):283–301.
40. Alwan F, Vendramin C, Liesner R, Clark A, Lester W, Dutt T, et al. Characterization and treatment of congenital thrombotic thrombocytopenic purpura. Blood. 2019;133:1644–51.
41. van Dorland HA, Taleghani MM, Sakai K, Friedman KD, George JN, Hrachovinova I, et al. The international hereditary thrombotic thrombocytopenic purpura registry: key findings at enrollment until 2017. Haematologica. 2019;104:2107–15.
42. von Krogh AS, Quist-Paulsen P, Waage A, Langseth ØO, Thorstensen K, Brudevold R, et al. High prevalence of hereditary thrombotic thrombocytopenic purpura in central Norway: from clinical observation to evidence. J Thromb Haemost. 2016;14:73–82.
43. Lotta LA, Wu HM, Mackie IJ, Noris M, Veyradier A, Scully MA, et al. Residual plasmatic activity of ADAMTS13 is correlated with phenotype severity in congenital thrombotic thrombocytopenic purpura. Blood. 2012;120:440–8.
44. Moatti-Cohen M, Garrec C, Wolf M, Boisseau P, Galicier L, Azoulay E, et al. Unexpected frequency of Upshaw-Schulman syndrome in pregnancy-onset thrombotic thrombocytopenic purpura. Blood. 2012;119:5888–97.
45. Scully M, Thomas M, Underwood M, Watson H, Langley K, Camilleri RS, et al. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. Blood. 2014;124:211–9.
46. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian apheresis study group. N Engl J Med. 1991;325:393–7.
47. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158:323–35.
48. Pereira A, Mazzara R, Monteagudo J, Sanz C, Puig L, Martínez A, et al. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: a multivariate analysis of factors predicting the response to plasma exchange. Ann Hematol. 1995;70:319–23.
49. Bendapudi PK, Hurwitz S, Fry A, Marques MB, Waldo SW, Li A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol. 2017;4:e157–64.
50. Coppo P, Schwarzinger M, Buffet M, Wynckel A, Clabault K, Presne C, et al. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. PLoS ONE. 2010;5: e10208.
51. Li A, Khalighi PR, Wu Q, Garcia DA. External validation of the PLASMIC score: a clinical prediction tool for thrombotic thrombocytopenic purpura diagnosis and treatment. J Thromb Haemost. 2018;16:164–9.
52. Cataland SR, Kourlas PJ, Yang S, Geyer S, Witkoff L, Wu H, et al. Cyclosporine or steroids as an adjunct to plasma exchange in the treatment of immune-mediated thrombotic thrombocytopenic purpura. Blood Adv. 2017;1:2075–82.
53. Froissart A, Buffet M, Veyradier A, Poullin P, Provôt F, Malot S, et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French thrombotic microangiopathies reference center. Crit Care Med. 2012;40:104–11.
54. Sun L, Mack J, Li A, Ryu J, Upadhyay VA, Uhl L, et al. Predictors of relapse and efficacy of rituximab in immune thrombotic thrombocytopenic purpura. Blood Adv. 2019;3:1512–8.
55. Kubo M, Sakai K, Yoshii Y, Hayakawa M, Matsumoto M. Rituximab prolongs the time to relapse in patients with immune thrombotic thrombocytopenic purpura: analysis of off-label use in Japan. Int J Hematol. 2020;112:764–72.
56. Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood. 2011;118:1746–53.
57. Westwood JP, Thomas M, Alwan F, McDonald V, Benjamin S, Lester WA, et al. Rituximab prophylaxis to prevent thrombotic thrombocytopenic purpura relapse: outcome and evaluation of dosing regimens. Blood Adv. 2017;1:1159–66.
58. Hie M, Gay J, Galicier L, Provôt F, Presne C, Poullin P, et al. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. Blood. 2014;124:204–10.
59. Al-Samkari H, Grace RF, Connors JM. Ofatumumab for acute treatment and prophylaxis of a patient with multiple relapses of acquired thrombotic thrombocytopenic purpura. J Thromb Thrombolysis. 2018;46:81–3.
60. Robertz J, Andres M, Mansouri Taleghani B, Koneth I, Binet I, Kremer Hovinga JA. Obinutuzumab in two patients suffering from immune-mediated thrombotic thrombocytopenic purpura intolerant to rituximab. Am J Hematol. 2019;94:E259–61.
61. Eskazan AE. Bortezomib therapy in patients with relapsed/refractory acquired thrombotic thrombocytopenic purpura. Ann Hematol. 2016;95:1751–6.
62. van den Berg J, Kremer Hovinga JA, Pfleger C, Hegemann I, Stehle G, Holbro A, et al. Daratumumab for immune thrombotic thrombocytopenic purpura. Blood Adv. 2022;6:993–7.
63. Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knöbl P, Wu H, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2016;374:511–22.
64. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019;380:335–46.
65. Peyvandi F, Cataland S, Scully M, Coppo P, Knoebl P, Kremer Hovinga JA, et al. Caplacizumab prevents refractoriness and

mortality in acquired thrombotic thrombocytopenic purpura: integrated analysis. Blood Adv. 2021;5:2137–41.
66. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: toward targeted therapy and precision medicine. Res Pract Thromb Haemost. 2019;3:26–37.
67. Völker LA, Kaufeld J, Miesbach W, Brähler S, Reinhardt M, Kühne L, et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv. 2020;4:3085–92.
68. Coppo P, Bubenheim M, Azoulay E, Galicier L, Malot S, Bigé N, et al. A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood. 2021;137:733–42.
69. Dutt T, Shaw RJ, Stubbs M, Yong J, Bailiff B, Cranfield T, et al. Real-world experience with caplacizumab in the management of acute TTP. Blood. 2021;137:1731–40.
70. Pascual Izquierdo MC, Mingot-Castellano ME, Kerguelen Fuentes AE, Peinado G-AJ, Cid J, Jiménez M, et al. Real-world effectiveness of caplacizumab vs standard of care in immune thrombotic thrombocytopenic purpura. Blood Adv. 2022;6:6219–27.
71. Goshua G, Sinha P, Hendrickson JE, Tormey C, Bendapudi PK, Lee AI. Cost effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood. 2021;137:969–76.
72. Di Minno G, Ravasio R. Cost-effectiveness analysis of caplacizumab in the new standard of care for immune thrombotic thrombocytopenic purpura in Italy. Grhta. 2021;8:43–52.
73. Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18:2496–502.
74. Scully M, Knöbl P, Kentouche K, Rice L, Windyga J, Schneppenheim R, et al. Recombinant ADAMTS-13: first-in-human pharmacokinetics and safety in congenital thrombotic thrombocytopenic purpura. Blood. 2017;130:2055–63.
75. Plaimauer B, Kremer Hovinga JA, Juno C, Wolfsegger MJ, Skalicky S, Schmidt M, et al. Recombinant ADAMTS13 normalizes von Willebrand factor-cleaving activity in plasma of acquired TTP patients by overriding inhibitory antibodies. J Thromb Haemost. 2011;9:936–44.
76. Jian C, Xiao J, Gong L, Skipwith CG, Jin SY, Kwaan HC, et al. Gain-of-function ADAMTS13 variants that are resistant to autoantibodies against ADAMTS13 in patients with acquired thrombotic thrombocytopenic purpura. Blood. 2012;119:3836–43.
77. Ercig B, Graça NAG, Kangro K, Arfman T, Wichapong K, Hrdinová J, et al. N-glycan-mediated shielding of ADAMTS13 prevents binding of pathogenic autoantibodies in immune-mediated TTP. Blood. 2021;137:2694–8.
78. Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2010;115:1500–11.
79. Rizvi MA, Vesely SK, George JN, Chandler L, Duvall D, Smith JW, et al. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome. Transfusion. 2000;40:896–901.
80. Chander DP, Loch MM, Cataland SR, George JN. Caplacizumab therapy without plasma exchange for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019;381:92–4.
81. Völker LA, Brinkkoetter PT, Knöbl PN, Krstic M, Kaufeld J, Menne J, et al. Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab. J Thromb Haemost. 2020;18:3061–6.
82. Riva S, Mancini I, Maino A, Ferrari B, Artoni A, Agosti P, et al. Long-term neuropsychological sequelae, emotional wellbeing and quality of life in patients with acquired thrombotic thrombocytopenic purpura. Haematologica. 2020;105:1957–62.
83. Alwan F, Mahdi D, Tayabali S, Cipolotti L, Lakey G, Hyare H, et al. Cerebral MRI findings predict the risk of cognitive impairment in thrombotic thrombocytopenic purpura. Br J Haematol. 2020;191:868–74.
84. Chaturvedi S, Oluwole O, Cataland S, McCrae KR. Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura. Thromb Res. 2017;151:51–6.
85. George JN. TTP: long-term outcomes following recovery. Hematol Am Soc Hematol Educ Program. 2018;2018:548–52.
86. Brodsky MA, Sukumar S, Selvakumar S, Yanek L, Hussain S, Mazepa MA, et al. Major adverse cardiovascular events in survivors of immune-mediated thrombotic thrombocytopenic purpura. Am J Hematol. 2021;96:1587–94.