



Immune thrombotic thrombocytopenic purpura: pathogenesis and novel therapies: a narrative review

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Background and Objectives: Immune thrombotic thrombocytopenic purpura (iTTP) is a rare, but potentially fatal blood disease, resulting from autoantibodies against A Disintegrin and Metalloprotease with Thrombospondin Type 1 Repeats, 13 (ADAMTS13). While major progress has been made in past decades concerning early diagnosis and management of iTTP, the mechanisms underlying the formation and the mechanism of action of these autoantibodies against ADMATS13 are still unknown. This review will provide a narrative review of pathogenesis and novel therapeutics of iTTP.

Methods: We did PubMed literature search using a combination of thrombotic thrombocytopenic purpura and treatment or pathogenesis from 1955 to November 2022. A total of 4,767 articles with full text were found and only relevant articles in English were further reviewed and summarized.

Key Content and Findings: We found that the primary mechanism underlying severe ADAMTS13 deficiency in patients with iTTP is autoantibody-mediated inhibition and/or accelerated clearance of ADAMTS13 metalloprotease. Other factors including allosteric regulation and post-translational modifications (i.e., glycosylation and citrullination, and arginine methylation, etc.) may affect ADAMTS13 secretion and function and also contribute to the pathogenesis of iTTP. The standard of care for iTTP today consists of therapeutic plasma exchange, anti-von Willebrand factor (vWF) caplacizumab, and immunosuppressives (e.g., corticosteroids and rituximab), known as the triple therapy, which has significantly reduced exacerbation and mortality rates.

Conclusions: We hope that the information provided in the review article helps better understand the pathogenesis of iTTP, which may guide design novel and more effective therapeutics for this potentially fatal disorder.

Keywords: A Disintegrin and Metalloprotease with Thrombospondin Type 1 Repeats, 13 (ADAMTS13); immune thrombotic thrombocytopenic purpura (iTTP); autoantibody; posttranslational modification; novel therapeutics

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Introduction

Immune thrombotic thrombocytopenic purpura (iTTP) is a rare, but potentially fatal blood disorder. It is caused by severe deficiency of a plasma metalloenzyme A Disintegrin And Metalloprotease with Thrombospondin Type 1

Repeats, 13 (ADAMTS13) activity (1-3). The incidence of iTTP ranges from 3–6 cases per million residents per year (4,5). Immunoglobulin (Ig) G-type autoantibodies bind and inhibit plasma ADAMTS13 activity; additionally, immune complexes may be cleared from circulation resulting in

Table 1 Literature search

Items	Specification
Date of search	Nov. 19, 2022
Databases and other sources searched	PubMed
Search terms used	Thrombotic, thrombocytopenic, purpura and pathogenesis, or thrombotic thrombocytopenic purpura and treatment
Timeframe	1955–November 2022
Inclusion and exclusion criteria	Only articles with full text in English are included for screening and small number of relevant articles are further reviewed
Selection process	First and senior authors

significantly reduced ADAMTS13 protein in some cases (6–9). The severe deficiency of plasma ADAMTS13 activity renders an inability to cleave newly released ultra-large (UL) von Willebrand factor (vWF) multimers which are anchored on endothelial surface (10–13) and circulating in blood (14–17). This results in an enhanced platelet adhesion and aggregation, and the formation of occlusive thrombi in small arterioles and capillaries, leading to systemic organ damage and even death (18,19). Following acute episode, patients may experience disease relapses (20,21), cognitive decline, depression (22), and increased risk of cardiovascular diseases (23,24), etc., as part of long-term complications.

While the mechanism underlying the autoimmunity resulting in the formation of ADAMTS13 antibodies is still not known, limited data available to date have demonstrated that polyclonal IgG autoantibodies appear to bind multiple domains of ADAMTS13 with the cysteine-rich and spacer domains being the most frequent targets of all (25). Current treatment of iTTP includes therapeutic plasma exchange (TPE), caplacizumab, and immunosuppressives (such as rituximab, corticosteroids, or other regimens) (26,27). This triple therapy has significantly reduced the exacerbation, relapse, and in-hospital mortality of iTTP (28–31). The present review summarizes some of these progresses concerning the pathogenesis and novel therapeutics of iTTP. We present this article in accordance with the Narrative Review reporting checklist (available at <https://aob.amegroups.com/article/view/10.21037/aob-22-29/rc>).

Methods

We conducted PubMed literature search using a combination of keywords thrombotic thrombocytopenic purpura and novel therapeutics or treatment from 1955

to November 2022. Of 4,767 articles published with full text, only small number of articles in English related to the topic were selected for further review and citation in this narrative review article (*Table 1* and *Figure 1*).

Discussion

Pathophysiology

The pathophysiology of iTTP has been extensively studied since the identification and molecular cloning of ADAMTS13 (1,32–34) and the development of several rapid ADAMTS13 activity assays (35–39). The International Society of Thrombosis and Haemostasis (ISTH) guidelines for the diagnosis and management of TTP state that in a proper clinical context plasma ADAMTS13 activity less than 10 units/dL (or <10 percent of normal) (40) confirms the diagnosis of TTP; ADAMTS13 activity greater than 20 units/dL (or 20 percent of normal) essentially rules out the initial diagnosis of TTP; however, plasma ADAMTS13 activity between 10 and 20 units/dL or (10–20 percent of normal) is considered to be a broadline value (5,27).

The only known function of ADAMTS13 is to cleave newly releases UL-vWF multimers anchored on endothelial cells. This proteolytic cleavage is essential for normal hemostasis (*Figure 2A*) (11–13). ADAMTS13 may also cleave vWF multimers at the sites of vascular injury. This prevents the formation of occlusive thrombi but without affecting normal hemostasis (41–43). Furthermore, ADAMTS13 may cleave circulating vWF multimers when exposed to high fluidic shear, such as in the bifurcated or narrowed portions of blood vessels (44–46). If plasma ADAMTS13 protease is severely deficient, primarily resulting from autoantibodies-mediated inhibition or accelerated clearance of ADAMTS13, the UL-vWF multimers or strings

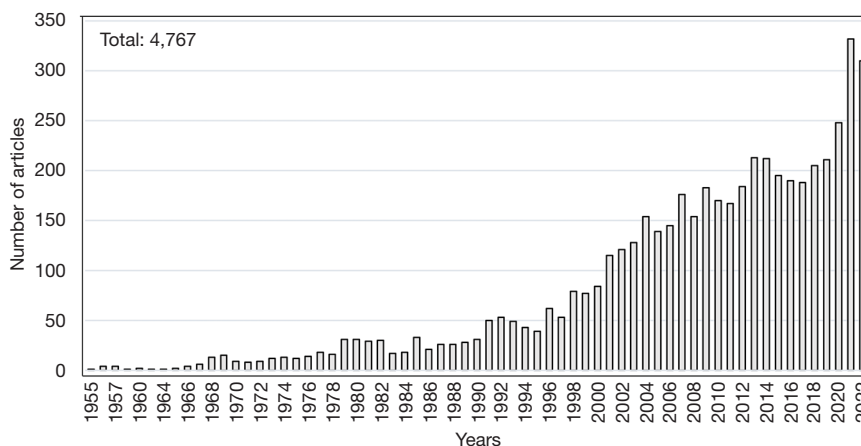


Figure 1 The number of articles published in TTP pathogenesis and treatment over the years since 1955. TTP, thrombotic thrombocytopenic purpura.

accumulate on the endothelial surface (*Figure 2B*) or at the sites of vascular injury, which recruit flowing platelets and form occlusive thrombi.

While severe deficiency of plasma ADAMTS13 activity may be necessary, it alone may not be sufficient to cause an acute episode of iTTP. Additional environmental or genetic factors may be required to trigger the disease. Infections (e.g., respiratory, or gastrointestinal), systemic inflammation (e.g., lupus), pregnancy (or postpartum), surgery (or trauma), and certain medications were often found to be associated with acute iTTP. The reason why a second hit is needed for a full-blown iTTP is not fully understood. It may be possible that a small amount of residual ADAMTS13 activity and/or other proteases such as neutrophil proteases (47) and plasmin (48) are sufficient to remove the UL-vWF strings from endothelial surface or at the sites of vascular injury at the basal levels. This proteolytic capacity may be overwhelmed when a large amount of vWF is secreted from endothelium as a result of an infection such as in the case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection (49-52) or trauma (53,54). Interestingly, in Baboon (55) or in some new born children (or neonates) (46,50,51,53,54,56), severe deficiency of plasma ADAMTS13 activity appears to be sufficient to cause an acute TTP, suggesting another potential genetic factor that might modify the susceptibility of TTP in these baboon or neonates.

Supporting this hypothesis comes from mutations in complement factor H (*CFH*) found in patients with hereditary TTP (57) or iTTP (8). A heterozygous or homozygous mutation in *cfh* and *Adamts13* deficiency

appear to play a synergistic role in causing thrombotic microangiopathy in mice, but either alone is not sufficient to cause a disease (6,58). In fact, elevated plasma levels of complement activation markers are commonly detected in patients with acute iTTP (7,9,59-63). Whether an inhibition of complement activation during acute iTTP would be therapeutically beneficial is yet to be determined. Anecdote case reports demonstrate the therapeutic efficacy of adding eculizumab to chronic relapsing iTTP (64,65).

Autoantibodies against ADAMTS13

Almost all adult iTTP patients are caused by IgG autoantibodies against ADAMTS13 (40,66), although the risk factors and underlying mechanism for the development of autoantibodies are not clear. Studies have shown that iTTP appears to be more common in young females, particularly African descents (67). The polyclonal anti-ADAMTS13 IgGs bind various domains of ADAMTS13 with the cysteine-rich and spacer domains being the most frequent targets. Additionally, approximately one third of patients may have IgG autoantibodies that bind other parts of ADAMTS13 protease. To date, there are a number of mouse and human monoclonal antibodies being developed or identified (*Figure 3A*). These are critical reagents for investigating the structure-function relationship and allosteric regulation of ADAMTS13 function.

Most inhibitory antibodies appear to bind the spacer domain (68-71) although the mechanism of inhibition remains to be elucidated. Hydrogen-deuterium exchange plus mass spectrometric (HX-MS) analysis demonstrates

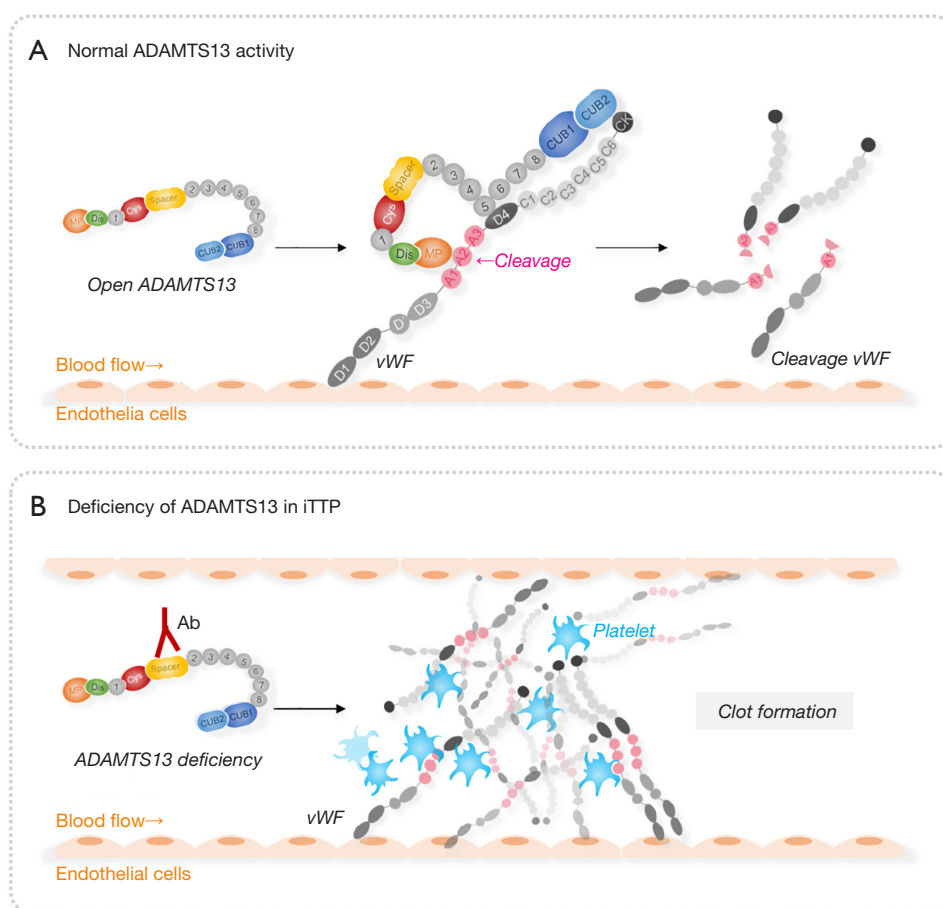


Figure 2 Mechanism of ADAMTS13 action in normal and iTTP. (A) Under normal conditions, UL-vWF multimers are released from activated or injured endothelial cells where they are rapidly cleaved by ADAMTS13 at the central A2 domain (Tyr¹⁶⁰⁵-Met¹⁶⁰⁶). This results in the formation of smaller vWF multimers that are hemostatic but not thrombogenic. (B) In iTTP, a functional ADAMTS13 is inhibited by an autoantibody, resulting in acquired deficiency of plasma ADAMTS13 activity. This leads to an accumulation of UL-vWF multimers on endothelial surface or at the site of vascular injury. The UL-vWF multimers attract circulating platelets and result in the formation of occlusive thrombi in small arterioles and capillaries. iTTP, immune thrombotic thrombocytopenic purpura; Ab, antibody; ADAMTS13, ADAM metallopeptidase with thrombospondin type 1 motif 13; Cys, cysteine-rich; Dis, disintegrin-like; MP, metalloprotease; UL-vWF, ultra-large von Willebrand factor.

that the anti-spacer domain antibodies, isolated from iTTP patients, bind 5 small flexible loops where vWF binds, suggesting that these antibodies may physically block the interaction between ADAMTS13 enzyme and its substrate vWF (69). An alternative hypothesis is also possible in which the binding of these antibodies to the spacer domain may result in a conformational change in the catalytic domain, thus affecting the cleavage efficiency of ADAMTS13 protease (72,73). More studies are needed to delineate the mechanism of antibody-mediated inhibition of ADAMTS13 activity.

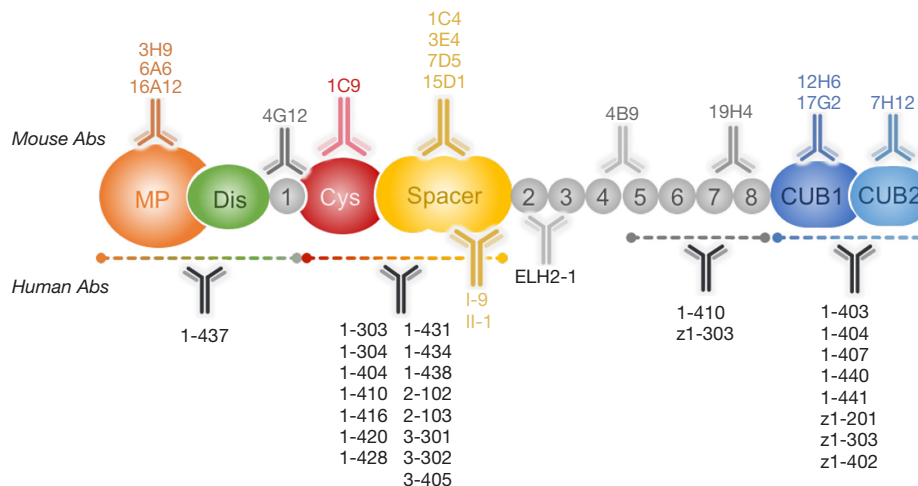
Unlike anti-spacer antibody, the antibodies that bind

the distal domains of ADAMTS13 such as T8-CUB (e.g., scFv4-3) or CUB (e.g., 17G2, 7H12 and 12H6) may induce conformational changes in ADAMTS13 (72,74,75), thus activating ADAMTS13 enzyme. However, how these polyclonal antibodies interact with ADAMTS13 resulting in inhibition of ADAMTS13 activity and/or accelerated clearance *in vivo* remains to be a subject of great interest for researchers.

Posttranslational modifications of ADAMTS13

Apart from vWF and antibodies targeting the C-terminal

A Antibodies against ADAMTS13



B Posttranslational modifications on ADAMTS13

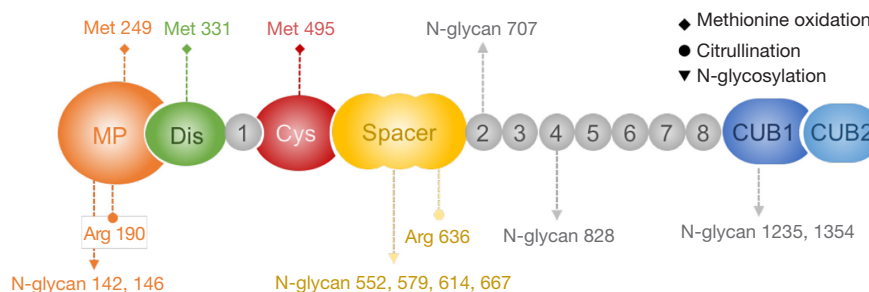


Figure 3 Anti-ADAMTS13 antibodies and potential post-translational modifications on ADAMTS13. (A) ADAMTS13 protein consists of 14 different domains: MP, Dis, 8 thrombospondin type 1 repeats (T1-T8), Cys, and spacer. The more distal domains contain two CUB domains (i.e., C1r/C1s and Uegf, Bmp1). Potential binding epitopes of mouse monoclonal antibodies against human recombinant ADAMTS13 (top) and human monoclonal antibodies isolated from patients with iTTP (bottom); (B) known or potential sites for post-translational modifications with oxidation (♦), arginine citrullination (●), and N-glycosylation (▼), etc. Ab, antibody; ADAMTS13, ADAM metalloproteinase with thrombospondin type 1 motif 13; Arg, arginine; Cys, cysteine-rich; Dis, disintegrin-like; Met, methionine; MP, metalloprotease.

domains that activate ADAMTS13, post-translational modifications on ADAMTS13 protein may also impact its secretion and functions. ADAMTS13 may be modified at posttranslational levels by oxidation, glycosylation, citrullination, fucosylation or mannosylation (76-80), and possible methylation (Figure 3B). Glycosylation is a process by which a carbohydrate is covalently attached to the target protein. Glycosylation plays a variety of critical roles in many cellular events ranging from protein secretion, signaling, and protein-protein interaction (77,80,81). Changes in glycosylation can modulate inflammatory responses, enable viral immune escape, promote cancer cell

progression or regulate cell death (82-84). N-glycosylation on ADAMTS13 has been shown to alter its secretion, conformation, and proteolytic activity (77,80). For instance, N146Q and N828Q mutants of ADAMTS13 exhibit a decreased secretion and proteolytic activity (77). It is also known that the loss of N-glycan in the T2-CUB region of ADAMTS13 where the molecular flexibility exists results in alteration of ADAMTS13 conformations (85). Citrullination may occur on arginine residues, which are converted to the citrullinated residues. This may impact ADAMTS13 protein structure, function, stability, and protein-protein interactions resulting from the loss of positive charges

in the arginine residues. The citrullination process is catalyzed by an enzyme, peptidyl arginine deiminase-4 (PAD4) (80,83,84,86). Citrullination process is involved in pathology of many autoimmune disorders including rheumatoid arthritis and multiple sclerosis and other thrombo-inflammatory disorders such as sepsis and venous thrombosis (79,87,88). A recent study has demonstrated that ADAMTS13 can be citrullinated by PAD4 *in vitro* and *in vivo* (88). Mass spectrometry localized the citrullinated residues to arginine 190 and arginine 636 on ADAMTS13, which is within the metalloprotease and spacer domain, respectively. The citrullinated ADAMTS13 exhibits a reduced proteolytic activity towards vWF substrates (88).

Methylation is another post-translational modification that may occur on arginine residues of ADAMTS13. This process is often catalyzed by protein arginine methylation transferase-1 (PRMT1), which catalyzes the transfer of a methyl group from a co-substrate S-adenosyl-L-methionine (SAM) to the guanidine nitrogen of a peptidyl arginine residue. PRMT1 performs over 80% of methylation activity in cells (89). Using MeMo and PRmePred web tool (90,91), we estimate approximately 35 asymmetric dimethylated arginines and 35 mono-methylated arginines on ADAMTS13. Whether one or several arginines on ADAMTS13 are methylated and how this posttranslational modification affects ADAMTS13 secretion and proteolytic function are under intense investigation in our laboratory.

Novel therapeutics

ISTH published the first guidelines for the diagnosis and management of iTTP (5,27). When a patient with highly suspected or confirmed iTTP based on clinical presentation (e.g., severe thrombocytopenia, microangiopathic hemolytic anemia and organ injury) or ADAMTS13 activity less than 10 units/dL, a combination of TPE, caplacizumab, and immunosuppressive (e.g., corticosteroids, rituximab, etc.), known as the triple therapy, should be given as early as possible (5,27,92). Such a therapeutic modality has been shown to significantly reduce the exacerbation and in-hospital mortality (29,93-95). As soon as the clinical diagnosis is made, emergent TPE should be initiated, followed by early caplacizumab and corticosteroids.

TPE is presumably removes IgG autoantibodies against ADAMTS13 (92) and damage-associated molecular patterns (DAMPs) such as S100A8/9 (96) and histone-DNA complexes (96) while replenishing the deficient ADAMTS13 enzyme (Figure 4A). Longitudinal study

demonstrated that TPE alone is not sufficient to remove all antibodies and supply sufficient amount of ADAMTS13 to overcome the inhibition, particularly in those with high-titer inhibitors (92).

Caplacizumab, an anti-vWF nanobody, that binds vWF-A1 domain and inhibits the adhesion of platelets to UL-vWF, thus inhibiting thrombus formation (97,98) (Figure 4B). This prevents further tissue damage while plasma ADAMTS13 activity remains low and inhibitors are present. Despite of daily plasma exchange and early administration of rituximab, it may take weeks, if not months, to eliminate anti-ADAMTS13 IgG production (99,100).

Rituximab, an anti-CD20 monoclonal antibody, should be prescribed to patients as early as possible to halt the production of anti-ADAMTS13 autoantibodies (Figure 4C), which accelerates the recovery of ADAMTS13 and prevents exacerbation and relapses (101-103).

Other emergent therapeutic products, including recombinant ADAMTS13 (104-106), gain-of-functional (GoF) and antibody-resistant ADAMTS13 variants (107), and platelet-delivered ADAMTS13 (43,108), are all under development. All these approaches are expected to overcome or bypass the inhibitory antibodies against ADAMTS13 in patients with iTTP. The first in human trial for hereditary TTP has been completed and reported (104). An infusion of recombinant ADAMTS13 at 5, 20, and 40 IU/kg body weight resulted in a dose-dependent increase of plasma ADAMTS13 activity and an increase of platelet counts from the baseline. No significant adverse events were observed. A similar trial of recombinant ADAMTS13 for the treatment of acquired iTTP in conjunction with TPE and other immunosuppressive therapies has been closed but data are not published (NCT03922308). These well-designed clinical trials hope to demonstrate pharmacokinetics, therapeutic efficacy, and safety of these potential treatments for both hereditary TTP and iTTP. GoF-ADAMTS13 variants have been created and shown to have an increased specific activity and significant resistance to autoantibody-mediated inhibition, which may be explored for therapeutic purpose (107,109). Alternative strategy to avoid autoantibody-mediated inhibition of recombinant ADAMTS13 is to pack recombinant ADAMTS13 inside platelet α -granules through genetic engineering (43) or *in vitro* uptake (108). In this case, autoantibody does not have a chance to interact with recombinant ADAMTS13 inside platelets. Upon activation, platelets release recombinant ADAMTS13 at the site where proteolysis of

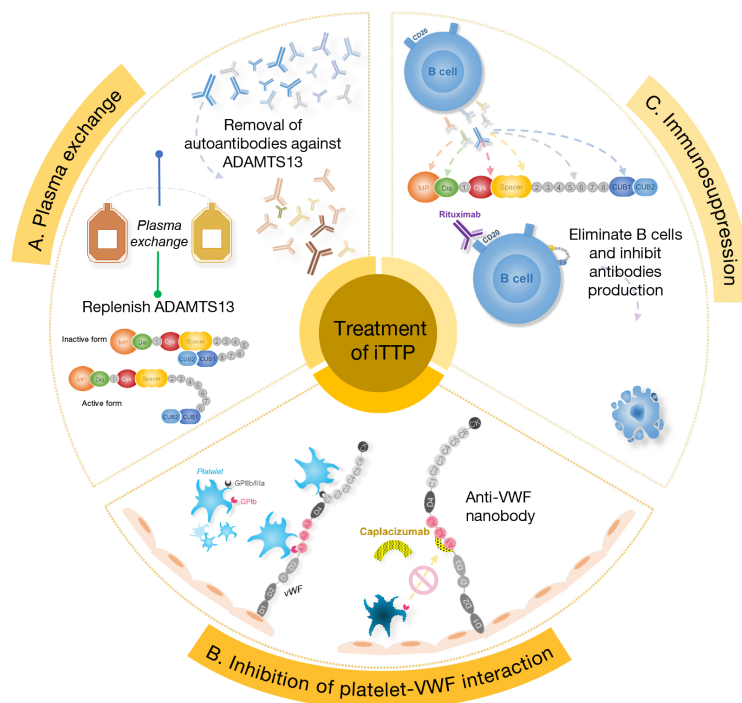


Figure 4 Therapeutic approaches for iTTP. (A) TPE removes autoantibodies against ADAMTS13 and other potential DAMPs while replenishing ADAMTS13 enzyme. (B) Anti-vWF nanobody inhibits thrombosis at sites of vascular injury. A mature vWF monomer (~250 kDa) is synthesized with domains in the order D'-D3-A1-A2-A3-D4-C1-C2-C3-C4-C5-C6-CK. Under high shear conditions, surface protein GP1b and GPIIb/IIIa on platelet separately interact to A2 domain and C1 domain of vWF that cause thrombus formation. Caplacizumab inhibits platelet-vWF interaction by binding to A1 domain of vWF, thus impeding platelet adhesion and thrombus formation. (C) Two monoclonal antibodies, rituximab and belimumab are the potential immunosuppressives for iTTP treatment. The main strategy aims to inhibit anti-ADAMTS13 autoantibodies production, thus accelerating disease recovery and preventing relapses. Belimumab directly blocks the B-lymphocyte stimulator which is secreted by myeloid cells to support B cells differentiation into plasma cells. Rituximab causes apoptosis of B cells by targeting CD20, thus inhibiting antibody production. ADAMTS13, ADAM metalloproteinase with thrombospondin type 1 motif 13; Arg, arginine; Cys, cysteine-rich; DAMPs, damage-associated molecular patterns; Dis, disintegrin-like; iTTP, immune thrombotic thrombocytopenic purpura; MP, metalloprotease; TPE, therapeutic plasma exchange; vWF, von Willebrand factor.

UL-vWF is most needed (43,108).

Conclusions

In summary, tremendous progresses have been made in past decades in our understandings of pathogenesis, diagnosis, and management of iTTP. However, the mechanisms underlying anti-ADAMTS13 autoantibody production and inhibition remain to be elucidated. Additionally, the mechanisms of allosteric or posttranslational regulations of ADAMTS13 activity continue to be the hot areas for future investigation in the field. Triple therapy including TPE, caplacizumab, and immunosuppression has significantly reduced exacerbation and mortality. However,

the long-term effects of this novel therapeutic strategy on cardiovascular complications, neurocognitive and behavioral changes, and quality of life are still not known.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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