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REVIEWS

TTP: From empiricism for an enigmatic disease to targeted molecular therapies

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Abstract

The 100th anniversary of the first description of Thrombotic Thrombocytopenic Purpura (TTP) as a disease by Dr. Eli Moschcowitz approaches. For many decades, TTP remained mostly a mysterious fatal condition, where diagnosis was often post-mortem. Initially a pentad of symptoms was identified, a pattern that later revealed to be fallible. Sporadic observations led to empiric interventions that allowed for the first impactful breakthrough in TTP treatment, almost 70 years after its first description: the introduction of plasma exchange and infusions as treatments. The main body of knowledge within the field was gathered in the latest three decades: patient registries were set and proved crucial for advancements; the general mechanisms of disease have been described; the diagnosis was refined; new treatments and biomarkers with improvements on prognosis and management were introduced. Further changes and improvements are expected in the upcoming decades. In this review, we provide a brief historic overview of TTP, as an illustrative example of the success of translational medicine enabling to rapidly shift from a management largely based on empiricism to targeted therapies and personalized medicine, for the benefit of patients. Current management options and present and future perspectives in this still evolving field are summarized.

†On behalf of the PROFILE consortium.

A BRIEF HISTORY OF THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

The 100th anniversary of the first description of a TTP case is approximately three years away. Despite this disease being known for almost one full century, the state-of-the-art knowledge in TTP had a slow initial evolution whereas during the last 30 years it has seen an explosive expansion.

In Manhattan 1924, Dr. Eli Moschcowitz attended a 16-year-old girl, who died after hospitalization for an acute illness displaying high fever, pallor, arm pain, petechiae, paralysis of the left arm and leg, and a preterminal coma. The autopsy revealed multiple 'hyaline' thrombi in the heart muscle vessels, the congested spleen, and kidneys. The disease cause and right treatment remained elusive, but Moschcowitz made an important note about an observation of one of his colleagues, Dr. Max Lederer, who had seen four other similar cases where, in contrast to Moschcowitz's case, all patients had clinical improvement following blood transfusions.[1] These observations were published later, and although they most closely resembled autoimmune or infectious haemolytic anaemia, they supported the view that some haemolytic pathologies could be treated by transfusion. This scenario was replicated later by Rubinstein et al, on another patient, with an associated rise in platelet counts and a drop in reticulocytes percentage.[2] The name 'Thrombotic Thrombocytopenic Purpura' was first used only in 1947 after another fatal case, where three autopsy findings stood out: hyaline thrombi, a severe thrombocytopenia and petechiae/purpura.[3] Accumulating cases made it possible to detect the main patterns of disease, with fast clinical deterioration and a pentad of unspecific symptoms first described by Amorosi and Ultman in 1966: fever, haemolytic anaemia with abundant schistocytes, thrombocytopenia (by consumption), purpura or other bleeding symptoms, neurologic signs (transient or permanent) and renal disease. The aetiology and pathophysiology remained elusive, with suggested causes including drugs, toxins, viral infections, and autoimmunity, all requiring more conclusive evidence. As a consequence, the disease was almost always fatal despite administration of various combinations of vitamins, adrenocorticotropin, corticosteroids, azathioprine, nitrogen mustard, anti-platelet agents such as dipyridamole or aspirin, heparin, streptokinase or splenectomy.[4] By the early 1960's, deficiency of an important factor in TTP patients and plasma therapy potential value was already recognized,[5] eventually leading TTP to be considered a congenital disease.[6] In the late 1970's Bukowski et al reported a small series of patients treated by exchange transfusion where remission rates rose to 60%[7] and Byrnes et al found through a series of exchange transfusions with different hemoderivatives that the missing factor was present in plasma.[8] Soon after, Gottschall et al described a series of 11 patients with a clinical diagnosis of TTP and their evolution in accordance with the type of blood products they received during exchange therapies.[9] Three patients who received platelet-poor whole

KEY POINTS

1. The main advances in the understanding of the century-old disease Thrombotic Thrombocytopenic Purpura (TTP) pathophysiology took place during the last three decades, and were successfully translated into diagnostic and therapeutic improvements.

2. Today, innovative technologies are driving profound changes in the diagnosis and treatment standards for TTP, making TTP an illustrative success of translational medicine.

3. In a foreseeable future, historical treatments such as therapeutic plasma exchange and plasma therapy for TTP may become obsolete with the upcoming inception of rhADAMTS13 for clinical use, the introduction of caplacizumab, and the extensive use of rituximab.

4. Knowledge gaps still exist, as it is yet not fully known how TTP patients develop cognitive impairments, and we must reinforce measures against cardiovascular risk factors and premature death, which are still prevalent in TTP patients.

blood all survived, whereas one out of three patients who received platelet-rich whole blood and two out of four patients treated by platelet concentrates with or without whole blood eventually died. Notably, the condition of one patient deteriorated within minutes after receiving platelet-rich whole blood. This last observation led to the general contraindication of platelet transfusion during TTP. These works slowly began to shape the pathogenesis of TTP, believed to be caused by a deficient inhibitor of platelet activation usually present in normal plasma.[10] Simultaneously these reports and others[10,11] added to the possibility of the disease being related to autoimmunity, because patients with systemic lupus erythematosus (SLE) were observed to often develop TTP, and because glucocorticoids used alone provided occasionally successful remissions.[7,8] Plasma therapy became the established gold standard treatment, as well as the usefulness of clinical follow-up by means of lactate dehydrogenase (LDH) and platelet counts, but no standardized regimen was yet established at the time, despite an observed correlation between recovery and dose of plasma administered.[11,12] During the early 1980s, Moake et al. helped understanding of the basic pathophysiology mechanism of TTP leap forward[13]: 'unusually large' (or ultralarge) von Willebrand factor multimers (UL-VWF) released from endothelial cells were found to accumulate in the plasma of patients with chronic relapsing TTP and a failure to process these UL VWF multimers was proposed to explain the disorder.[13]

The year 1991 marked the beginning of the modern TTP treatment era. Plasma Exchange (PEX) was shown to be superior to plasma infusions for successful remission

of the majority of TTP patients, moving the historically low survival rates of 10%–20% up to ~80% and firmly establishing an effective first-line treatment.[14,15] Between 1996 and 1998, knowledge in TTP exploded: first in 1996, the Swiss group of Furlan et al. [16] and the American group of Tsai [17] for the first time purified from plasma a metalloprotease specifically cleaving VWF (VWF-Cleaving Protease, VWF-CP, which would later become known as ADAMTS13); second, in 1997, Furlan et al. published the first case report of severe VWF-CP deficiency in a TTP patient[18]; third, in 1998, the same groups published in the same issue of the New England Journal of Medicine the first reports of severe VWF-CP deficiency in TTP cohorts.[19,20] Since 1998, several studies worldwide have confirmed the role of this VWF-CP/ADAMTS13 deficiency in TTP, the main mechanisms of ADAMTS13 deficiency were uncovered,[20–22] ADAMTS13 was cloned, recombinant ADAMTS13 was produced and characterized,[23] and further molecular structural insights were discovered, namely a conformational plasticity of ADAMTS13 (generally referred to 'open/closed conformation').[24–27] These stimulating and promising discoveries prompted clinicians, biologists and researchers to work together. These synergistic collaborations resulted in/from the establishment of local or national TTP patient registries and thrombotic microangiopathy (TMA) reference centres with well-organized and characterized biobanks, which have been a critical element driving forward all this knowledge. The main TTP local or national registries today include the registries of Canada, Oklahoma (USA), Italy, United Kingdom, France, Japan, Switzerland and Australia.[28–36] There is a large contrast between the sparsity of milestones in the first seven decades and the explosive number of ground-breaking achievements in the field done within the last three decades (Figure S1), namely:

1. TTP was distinguished from other closely resembling TMAs (notably Haemolytic Uremic Syndrome, HUS).[19,20]
2. Two forms of TTP were identified, with distinct mechanisms: congenital or hereditary TTP (cTTP or hTTP),[21] and acquired TTP (aTTP).[18–20,37]
3. ADAMTS13 was identified as the VWF-CP and cloned for recombinant protein production.[23]
4. ADAMTS13 activity assays were developed and refined. The first assays were laborious, involving the mixing of patient plasma with healthy donors' plasmas to detect the presence of ADAMTS13 inhibitors. This was done by means of incubation of these mixtures with barium chloride and dialysis against a denaturing agent, running the resulting VWF multimers in agarose gels and subsequently immunoblotting to assess cleavage of the multimers[19] and/or to detect the presence or absence of specific VWF cleavage products.[20] These were succeeded by other less cumbersome assays, such as the ELISA collagen binding assay,[38] and later the FRETS-vWF73 assay,[39] the current gold standard. Other promising assays are still being developed and validated.[40]

5. Epitope mapping studies of immune-mediated TTP (iTTP) patients' autoantibodies have progressively revealed that in the majority of patients the spacer domain of ADAMTS13 is targeted by autoantibodies.[41–43] Several domains of ADAMTS13 may be targeted simultaneously in almost any combination [44–47]; nonetheless, anti-spacer antibodies, when present, normally constitute the main bulk of the autoantibodies' mixtures in iTTP patients.[45,47–49]
6. The long-term description of patients' outcome following the acute phase, leading to consider TTP as a chronic relapsing disease.[15,50,51]
7. Successful new treatments with profound impacts for relapse prevention and disease management were introduced:
   a. rituximab used as first-line adjunctive treatment for iTTP patients or as pre-emptive treatment[52];
   b. more recently, caplacizumab as an adjunctive treatment in iTTP[53–56];
   c. the ongoing development of a therapeutic, recombinant human form of ADAMTS13 (rhADAMTS13).[57]

The intense research of the last decades led to several new players that introduced progressive but important changes in the field. Consequently, the terminology has also changed, with official terms being introduced in 2017.[58] Important terms defined in this consensus report included: 'immune-mediated TTP' (iTTP) now used for aTTP cases where there is proof of the immune system's involvement (i.e. presence of detectable autoantibodies); 'remission', 'exacerbation' and 'refractoriness'.[58] More recently, as TTP entered in the era of targeted therapies and precision medicine, new definitions incorporating ADAMTS13 activity as a decision-making criterion became necessary. Besides 'clinical response' (a recovery of platelets and LDH levels, with exacerbations still possible) and 'clinical remission' (a more definitive clinical response lasting at least 30 days after PEX and caplacizumab are stopped, or improved ADAMTS13 activity ≥20%, whichever occurs first), response to new standards of care now uses 'ADAMTS13 response', either 'partial' (ADAMTS13 activity detectable but below normal values) or 'complete' (normal ADAMTS13 activity). This new terminology reflects the need to address more systematically than before the autoimmune component of the disease, and the increasing use of B-cell immunomodulators (mostly rituximab) front-line.[59,60]

TTP AS WE KNOW IT TODAY – WHERE ARE WE?

An ADAMTS13 activity <10% (or <10 IU/dl) is the most specific biomarker for TTP.[61] It leads to accumulation of UL-VWF multimers, and can be either because of: (a) a hereditary set of (autosomal recessive) mutations that directly impair activity, synthesis, or secretion of the protease (cTTP, ~5% of cases),[21,62] with clusters identified in several regions of the globe[63–65]; or (b) due to an acquired impairment because of developed autoantibodies against ADAMTS13 (iTTP, ~95% of all cases).[30,34,66] It can occur at any age (9% childhood-onset TTP

and 91% adult-onset TTP) with a general female-to-male ratio of 2:1 in the immune-mediated form. The relative incidences of cTTP and iTTP in the different age groups show some contrast: 33% of childhood-onset TTP cases are cTTP, while only 3% of adult-onset TTP cases are cTTP. Almost all adult-onset cTTP cases are detected in women during pregnancy or other obstetrical conditions (miscarriage or stillbirth), where the prevalence of cTTP was found surprisingly high, reaching 50% to 66% of cases.[67–69] Multimeric VWF (including UL-VWF)

exists within Weibel–Palade bodies of endothelial cells and α-granules of platelets, and multimers are secreted to the blood-stream upon stimuli that activate the endothelium.[70] The VWF molecule is a force sensor, sensitive to the shear stress generated by blood flow. When shear stress is high enough to extend the VWF A2 domain, cleavage by ADAMTS13 occurs. With little to no ADAMTS13 activity, UL-VWF remains large in size with potent pro-thrombotic effects (Figure 1).[71] Decreased ADAMTS13 activity and antigen levels are natural
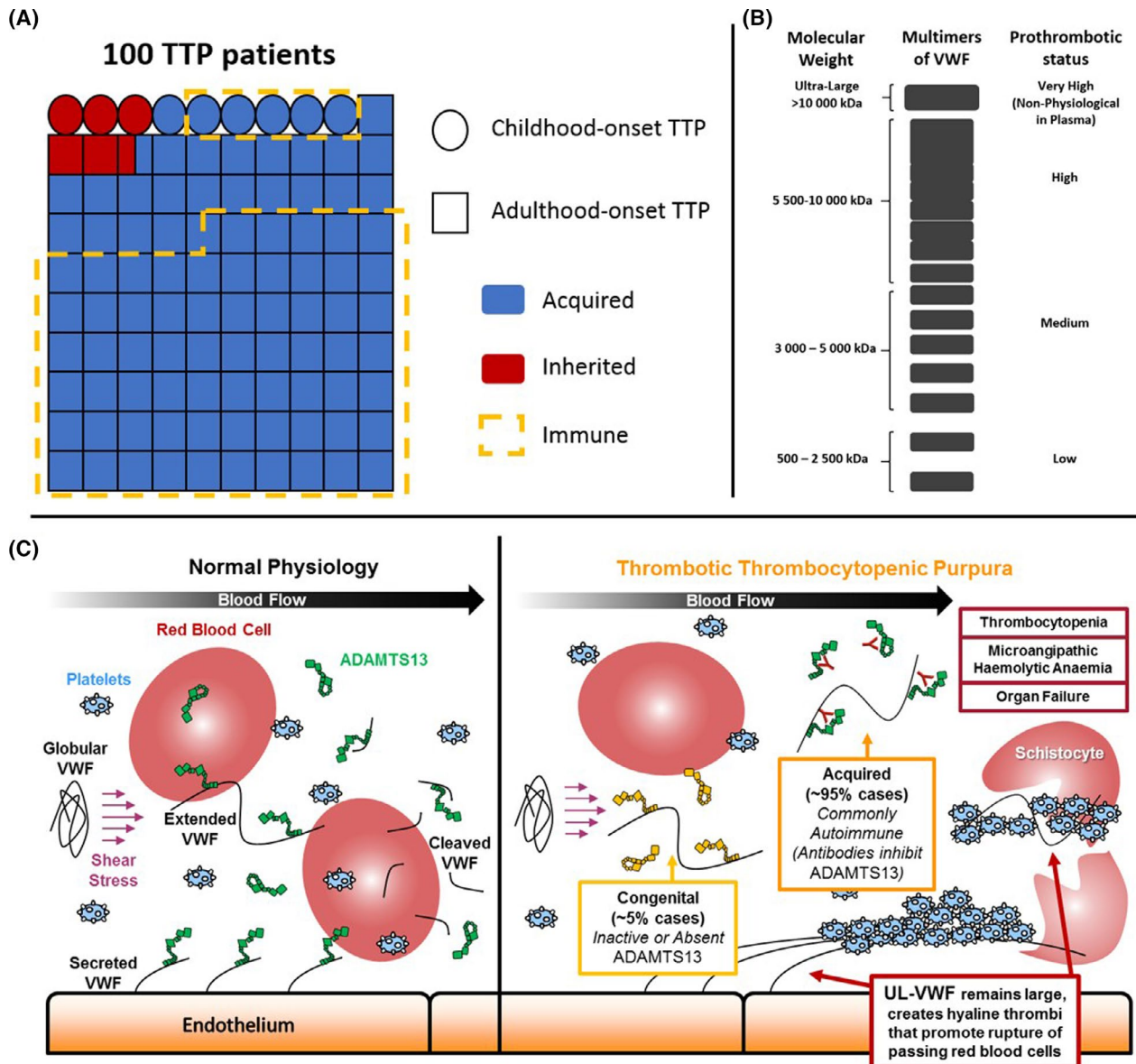
FIGURE 1 A representation of current Thrombotic Thrombocytopenic Purpura (TTP) epidemiology and its main mechanisms. (A) An overview of a population of 100 TTP patients and the likely distribution of the different types of TTP is shown (adapted from reference 69). (B) The multimeric size distribution of von Willebrand factor (VWF; adapted from reference 71). (C) Comparison between normal physiologic conditions of blood flow and TTP. The basic mechanisms of disease are shown, as well as the characteristic signs and symptoms. The relative sizes of ADAMTS13, autoantibodies, VWF multimers and blood cell components is not to scale. In physiologic conditions, functional ADAMTS13 (green ADAMTS13 molecules) cleaves [unusually large (UL)]-VWF multimers that are secreted from endothelial cells and unravel under high shear stress conditions. In TTP, ADAMTS13 is not functional (activity <10%) either due to mutations (yellow ADAMTS13 molecules)/lack of its secretion (cTTP), or because of autoantibodies that target functional ADAMTS13 and directly inhibit its activity and/or clear it from circulation (iTTP). In TTP, UL-VWF multimers are not processed and this facilitates platelet recruitment and thrombosis within the circulation, as well as red-blood-cell damage (red blood cells get fragmented and will appear as schistocytes in a blood film)

during pregnancy, and are caused by the increased secretion of VWF antigen which occurs during a normal pregnancy (prominently during the second and third trimesters) and/or hormonal changes.[72] Additionally, increased levels of inflammation (particularly present in the case of infections) may also concur to tilt the balance of the ADAMTS13-VWF axis.[73,74] In line with these statements, a remaining enigmatic aspect of cTTP pathophysiology is the absence of systematic correlation between genotype and phenotype, as illustrated by some families where certain members are severely affected and others with the same allelic mutations on *ADAMTS13* gene reach an advanced age with no attacks. Such observations support the existence of triggers but also modifiers in cTTP.[75] The total volume of platelets in circulation of a normal adult is typically only 10–20 ml, making it easy to develop pronounced thrombocytopenia through VWF–platelet aggregates.[76] More rarely however, the development of TTP signs and symptoms can be asynchronous, as the sequestration of platelets may occur in sites with lower shear stress without causing haemolytic anaemia, and/or the thrombus may be localized to a critical site, causing a life-threatening thromboembolic event before overt heamolytic anaemia or thrombocytopenia.[77] Lesions tend to occur in the heart, pancreas, kidney and the brain, without extensive necrosis, suggesting transient occlusion of the blood vessels in these sites.[78]

A delay in the management of TTP worsens its prognosis. Several ADAMTS13 assays exist,[79,80] and having the ADAMTS13 activity results early at presentation would allow a fast and effective distinction of TTP from another TMA. Since ADAMTS13 tests are not always directly available in all healthcare facilities,[80] time lags usually exist[81] and therefore the initial diagnosis of TTP is frequently a clinical diagnosis. To assist the clinician in predicting the ADAMTS13 activity level, clinical score systems have been developed.[31,82,83] Among the most popular are the French Score, set out by the French TMA Reference Center (CNR-MAT),[31] and more recently the PLASMIC Score.[83] The difference between both scores is that the French Score presupposes that patients have a TMA with no associated condition. Clinical experience and awareness of TTP as a possible diagnosis is essential to prevent misdiagnosis, delayed treatment[84,85] and adverse outcomes owing to delayed treatment.[86] This aspect is of particular importance at a time when new standards of care started early in the course of disease allow survival of virtually all patients.[87,88]

MILESTONES IN TTP TREATMENT: MEET THE NEW PLAYERS

Management of the acute phase: A new standard of care addressing the three pillars of iTTP pathophysiology

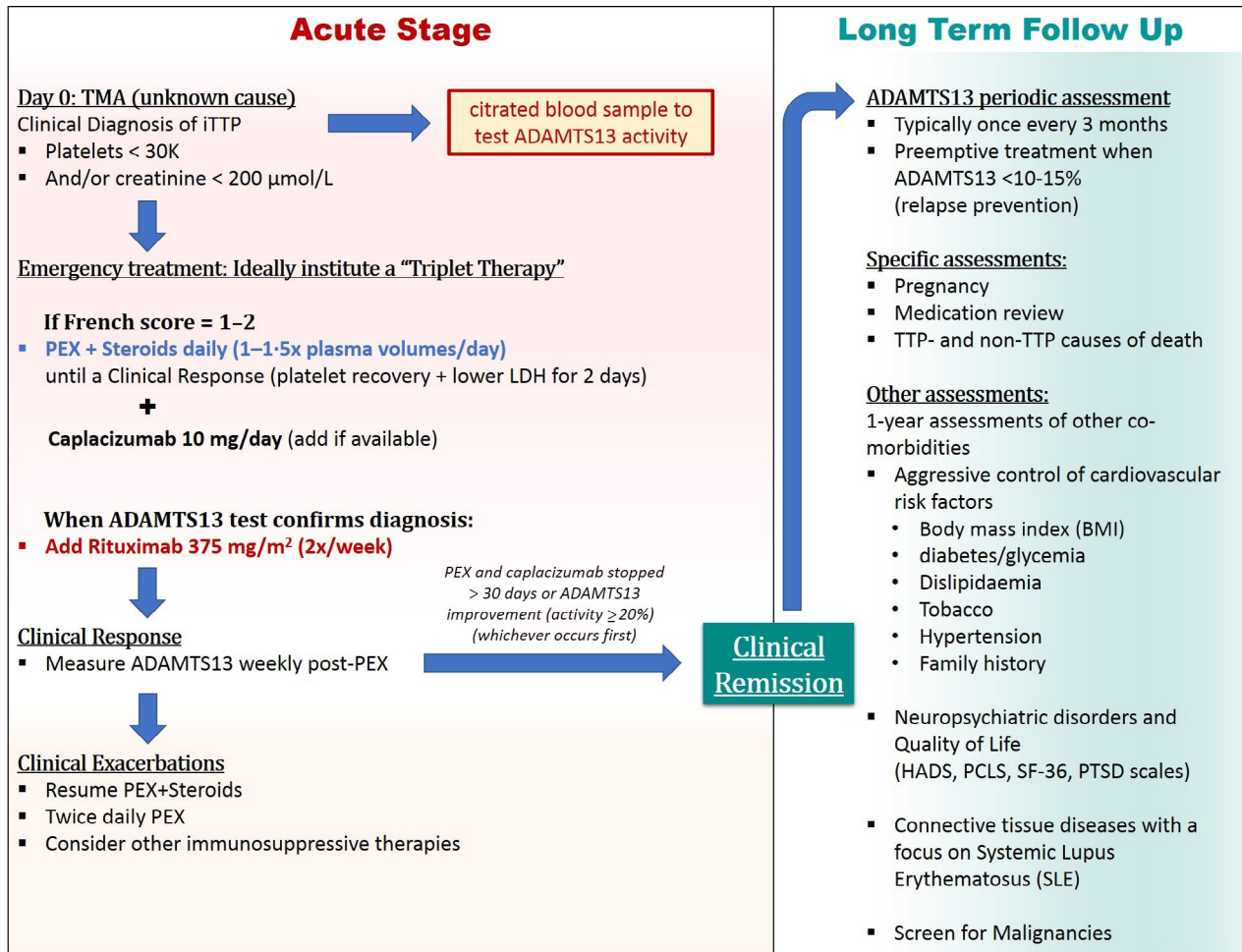Very few randomized studies with definitive conclusions have been performed in the field of TTP due to the rarity of the disease. Indeed, its management is largely based on empiricism and clinical experience that translated in recent experts' recommendations.[58–60]

The standard of care (SOC) for TTP has historically relied on plasma therapy, particularly plasma infusions for cTTP cases, and PEX for iTTP cases.[76] The prominent number of iTTP cases historically set the rationale for immunosuppression with corticosteroids front-line together with PEX in the acute phase. Rituximab, a B-cell-depleting monoclonal antibody, has moved from a salvage therapy in cases of refractory TTP or exacerbations[89] to front-line adjunctive therapy.[90,91] It takes on average two weeks for its clinical effects to follow,[52,92] and has very limited adverse effects reported so far.[92,93] After remission, relapses are quite common in iTTP patients and they may happen several years after a durable remission period.[50] Overall, up to 40% of patients with iTTP were reported to relapse during the first 7.5 years with the traditional SOC.[51] However, further analyses of historical control groups managed before the era of rituximab reported higher relapse rates, ranging from 57% at two years to 74% at seven years.[90,94] The systematic assessment of ADAMTS13 activity following the acute phase could refine the risk of relapse. Before the systematic use of rituximab, up to 40% of patients remained with an undetectable ADAMTS13 activity following clinical recovery, and among these patients almost 40% clinically relapsed within one year.[95] Based on these observations, strategies aimed at preventing relapses by means of immunomodulation proved fruitful, and the addition of rituximab as an early adjunctive therapy front-line showed to: (a) shorten the duration of PEX and hospitalizations by seven days; (b) lead to more durable improvements of ADAMTS13 activity; and (c) bear positive impacts on short-term remission and long-term relapse-free survival, with notably one-year relapse-free survivals of 100%.[52,91,96,97]

Caplacizumab is a nanobody that targets the interaction between UL-VWF multimers (VWF A1 domain) and platelets' glycoprotein Ib. The drug was first developed as an antithrombotic agent in the context of myocardial infarction, but greater interest has soon been paid to its therapeutic potential in TTP, and development for the first indication has since been discontinued. Instead, it was approved for acute iTTP treatment in adjunction to SOC.[55,98] In both clinical trials that served for the approval[53–56] as well as in real-world settings, caplacizumab led to faster platelet count recovery and reduced the time for a more durable clinical response, as well as the number of PEX rounds, and hospitalization time, despite the early use of rituximab.[88,99] Caplacizumab could prevent unfavourable outcomes, including death, refractoriness and exacerbations.[53,87,88,99,100] These benefits are attained at the expense of manageable minor bleeding events.[88] Whether caplacizumab has a long-term benefit on neurological complications associated with iTTP remains to be evaluated. Therefore, even considering the decrease in the cost of SOC, the addition of caplacizumab should increment the cost of a single iTTP episode by ~three- to fourfold,[101] which represents a limitation in the use of this new agent. As a result, caplacizumab is not

available in all countries. Lastly, one should consider caplacizumab as a suspensive agent protecting patients until immunosuppression improves ADAMTS13 activity. On the other hand, the price of caplacizumab recognizing its innovative nature should be balanced with the improvement of survival rate in a disease involving young patients.[87,102] As real-world evidence suggests that caplacizumab may be discontinued when ADAMTS13 activity reaches 20% or even 10% activity,[88,103] trials are ongoing to personalize caplacizumab treatment on the basis of ADAMTS13 activity (NCT04720261). Taken together, these new regimens associating systematically PEX, immunosuppression with corticosteroids and rituximab, and caplacizumab front-line allow achieving impressive survival rates of >95%, far surpassing the historical survival rate of 80%–85% provided by PEX and steroids for 30 years, while alleviating substantially the burden of care.[87,88,99] In line with these statements, intensive salvage regimens including twice-daily PEX, boluses of cyclophosphamide and splenectomy at the acute phase for highly resistant patients should become rare indications while front-line rituximab and caplacizumab are increasingly used.[104] Figure 2 presents the course of a patient with suspected/proven iTTP in a hospital with optimal resources.

Acute Stage

Day 0: TMA (unknown cause)
Clinical Diagnosis of iTTP
- Platelets < 30K
- And/or creatinine < 200 μmol/L

→ citrated blood sample to test ADAMTS13 activity

Emergency treatment: Ideally institute a "Triplet Therapy"

If French score = 1–2
- **PEX + Steroids daily (1–1·5x plasma volumes/day)**
  until a Clinical Response (platelet recovery + lower LDH for 2 days)

  +

  Caplacizumab 10 mg/day (add if available)

When ADAMTS13 test confirms diagnosis:
- **Add Rituximab 375 mg/m^2 (2x/week)**

Clinical Response
- Measure ADAMTS13 weekly post-PEX

Clinical Exacerbations
- Resume PEX+Steroids
- Twice daily PEX
- Consider other immunosuppressive therapies

PEX and caplacizumab stopped > 30 days or ADAMTS13 improvement (activity ≥ 20%) (whichever occurs first)

Clinical Remission

Long Term Follow Up

ADAMTS13 periodic assessment
- Typically once every 3 months
- Preemptive treatment when ADAMTS13 <10-15% (relapse prevention)

Specific assessments:
- Pregnancy
- Medication review
- TTP- and non-TTP causes of death

Other assessments:
1-year assessments of other co-morbidities
- Aggressive control of cardiovascular risk factors
  - Body mass index (BMI)
  - diabetes/glycemia
  - Dislipidaemia
  - Tobacco
  - Hypertension
  - Family history

- Neuropsychiatric disorders and Quality of Life (HADS, PCLS, SF-36, PTSD scales)

- Connective tissue diseases with a focus on Systemic Lupus Erythematosus (SLE)

- Screen for Malignancies

FIGURE 2 The course of a patient with suspected/proven immune-mediated Thrombotic Thrombocytopenic Purpura (iTTP) in a hospital with optimal resources. Acute stage: if the patient suffers from a thrombotic microangiopathy without any apparent cause, a clinical score should be used to estimate ADAMTS13 levels and a citrated blood sample taken for actual ADAMTS13 activity assessment at the day of presentation (Day 0). The French Score takes into account thrombocytopenia and creatinine values, scoring +1 for each if present. A score of 2 indicates high probability of ADAMTS13 < 10%.[31] In this case, a triplet regimen with daily PEX + steroids and daily caplacizumab is instated. If the clinical score is 1, TTP should still be suspected and PEX + steroids and daily caplacizumab should be initiated and kept until the ADAMTS13 activity test results from Day 0 arrive. If ADAMTS13 ≥ 10%, this is suggestive of an alternative diagnosis. If ADAMTS13 < 10%, the diagnosis of iTTP is confirmed, and rituximab is added (usually by day 4 following PEX initiation). This regimen is kept until a clinical response ensues for two days, at which point PEX is stopped, but the remaining therapies continue, with weekly assessments of ADAMTS13 activity. Caplacizumab may be stopped once adequate ADAMTS13 responses are achieved (>20% or >10%).[88,103] Long-term follow-up: the focus shifts to preventing relapses and long-term morbidity, with periodic assessments of ADAMTS13 activity (typically every three months, with pre-emptive treatment if needed), and yearly assessments to control cardiovascular risk factors, assessment of neuropsychiatric disorders and improvement of quality of life as well as other specific assessments (e.g. pregnancy planning in the case of female patients of childbearing age)

After the acute phase: How we learnt to prevent long-term relapses

Upon sustained clinical remission achievement, management proceeds with a follow-up focused on relapse prevention. Relapses are associated with ADAMTS13 deficiency[105]; therefore ADAMTS13 activity should be measured in adequate time intervals, being tightened if required. Our practice is to measure ADAMTS13 once every three months for years after the acute phase. Although no formal recommendations have been issued, our practice is to offer a lifelong follow-up of ADAMTS13 activity, with a reduction of monitoring only after typically five years of treatment-free survival with normal ADAMTS13 activity. If ADAMTS13 activity drops to values <10–15%, pre-emptive rituximab is usually prescribed, allowing improvement in ADAMTS13 activity in 85% of cases.[94]

More on long-term follow-up

During long-term follow-up after recovery, iTTP patients have increased premature death and multiple major morbidities, including increased body mass index (BMI), hypertension, major depression, diabetes and chronic kidney disease.[106,107] Notably, up to 30% of iTTP survivors suffer from severe depression and 20% display extremely low/borderline cognitive ability.[107] Age has negative impacts both in the short term (atypical neurological presentation and delayed diagnosis), but also in the long term, as older survivors show increased long-term mortality that increases for every 10 years of age range.[108] Besides iTTP-related deaths, cardiovascular complications are prevalent in iTTP survivors, and are the leading primary cause of death (~28%), followed by malignancy (~21%) and infection (~14%), while other/unknown causes represent 10% of cases.[109] The incidence of strokes in iTTP survivors is fivefold higher than in the general population, and is associated with lower ADAMTS13 activity during remission.[110] In this setting, it becomes important to evaluate and control these added risk factors during follow-up to improve life expectancy and quality of life (QoL) of TTP survivors (Figure 2).

A large proportion of adulthood-onset cTTP is found in obstetric patients.[67–69] Data from the Japanese TTP registry shows that patients diagnosed with cTTP before pregnancy had prior planning consisting of ADAMTS13 activity monitoring and prophylactic plasma infusions throughout pregnancy, allowing for significantly higher live birth rates.[111] The authors suggest initiating prophylactic treatment immediately after conception because patients experience subclinical symptoms that are preventable by prophylactic treatment and the risk of foetal complications and death increases after 20 weeks of gestation. Plasma infusions have inherent limitations, and may be insufficient to prevent gestation complications in cases of uncontrolled cTTP before conception.[111] In this context, it becomes fundamental to identify asymptomatic family members of cTTP patients (especially sisters of childbearing age).

Of special note, obstetric iTTP is a subpopulation still in need of clearly defined strategies for pre-emptive measures and safe TTP treatments in this setting. Rituximab has been used before pregnancy as a pre-emptive treatment, and women are advised to wait six to nine months after administration before conceiving[112]; some have become pregnant before this without any major adverse effects reported to date.[68] ADAMTS13 activity should be assessed at preconception as it is predictive of pregnancy outcome. Normal ADAMTS13 activity is typically associated with an uneventful pregnancy, and ADAMTS13 assessments through pregnancy usually disclose persistently normal values. Patients with a severe ADAMTS13 deficiency are exposed to clinical relapses with foetal loss and require pre-emptive measures before conception. On the other hand, patients with a partial ADAMTS13 deficiency have the most unpredictable scenario and require at least monthly ADAMTS13 assessments to clarify the prognosis. Patients who experience a severe drop in ADAMTS13 activity during pregnancy require pre-emptive measures including PEX and steroids. Rituximab is ideally reserved for the post-partum period owing to lack of safety evidence.[113]

A new hope: The recombinant human ADAMTS13 (rhADAMTS13)

ADAMTS13 activity deficiency is a direct cause of TTP. This sets a rationale for using treatments based on direct enzyme replacement of ADAMTS13. In $Adamts13^{-/-}$ mice where clinical features of TTP are reproduced through overload of VWF as an additional trigger, administration of rhADAMTS13 allowed for clinical and haematological features to be reverted.[114] A first-in-human clinical trial to assess the safety of a single dose of rhADAMTS13 in cTTP patients has been performed and key findings included: (a) a similar pharmacokinetic profile to the wild-type enzyme found in plasma of healthy donors; (b) tolerability in the doses tested (5, 20 or 40 U/kg); and (c) no signs of immunogenicity after 28 days of exposure.[57] The efficacy of rhADAMTS13 for cTTP is now being tested in several phase 3 studies (NCT04683003 and NCT03393975), both as prophylactic and on-demand treatment, and their outcomes are eagerly anticipated.

The most recent data accumulated by the international cTTP registry has shown that the current standards of management of cTTP patients are far from optimal.[115] On top of a median 12-year gap between disease onset and clinical diagnosis, 28% of cTTP patients experienced premature thromboembolic events until enrolment in the cohort, including stroke, transient ischaemic attacks and myocardial infarctions. Incidences occur in all age groups and increase with age: in 50% or more of patients aged >40–50 or >50 years old at least one thromboembolic event has been experienced. Additionally, other neurologic conditions (headaches, mental and depressive disorders,

epilepsy) were common, and 25% of patients had renal insufficiency at the time of enrolment and end-organ damage. Despite this, 71% of patients were receiving regular prophylactic treatment, almost all with plasma products, with the median interval of regular treatments at 14.0 days (range: 2–75 days). The remaining 29% received only on-demand treatment, and the median time of treatment for acute events was seven days, most episodes being associated with a trigger (notably infections, alcohol excess in men, and pregnancy in women).[115] The plasma half-life of plasma-infused ADAMTS13 is two to four days,[116] patients typically reaching undetectable levels by days 7–10 after infusion of two to four units of plasma.[115,117] This leaves time gaps of a few days to weeks where cTTP patients become again vulnerable to (cumulative) end-organ damage and other events. This is apparent by the frequency of acute manifestations, with a median of 0.1 acute episodes/patient/year (range: 0.02–9 acute episodes/patient/year).[115] Importantly, the UK group reported that stroke incidence can be reduced with prophylactic therapy rather than on-demand therapy,[118] prompting to question whether all patients should always be receiving active prophylactic management instead. Yet, not all patients are willing or able to submit themselves to the burden of a tight schedule of prophylactic plasma regimens.[119] Further, 11% of patients in the international cTTP registry had a reported transfusion-transmitted viral disease,[115] and allergic reactions are also frequent, although manageable.[111] The recently published experience of the UK,[118] Swiss[119] and Japanese[120] TTP registries are all convergent: management standards in cTTP must be improved. RhADAMTS13 will allow refinements in the prophylactic regimens used in cTTP: a tighter prophylactic regimen with correct dosing of a pure form of ADAMTS13 will become available, may allow treatment to be continued at home, and may bring the possibility to prevent short-term and long-term comorbidities, as well as the possibility of applying a series of more standardized, yet personalized protocols, for example, depending on the mutations present, age of onset, or frequency of acute events.[121,122]

In iTTP, the scenario for applying rhADAMTS13 is different. The already-ongoing immune response of the patient, the different titres of autoantibodies, and the different ADAMTS13 domains targeted in each individual case will pose challenges. In *in vitro* studies of iTTP patient samples, and also in a rat model of iTTP based on injection of polyclonal goat anti-human ADAMTS13 antibodies, it was possible to override the antibodies with wild-type high-dose rhADAMTS13 and replenish enzyme activity leading to successful treatment of iTTP in these rats.[123–125] Because of these encouraging preclinical results, a clinical trial is currently ongoing to assess the efficacy and safety of wild-type rhADAMTS13 in addition to SOC in aTTP patients (SOAR-HI Trial, NCT03922308). Hurdles regarding standardization of treatment are expectable: dosing schedules and regimens may need to be tailored to each patient. This can likely be improved upon with rhADAMTS13 mutant variants resistant to a large fraction of the patients' autoantibody mixtures,[126] as long as rhADAMTS13 intrinsic activity is not lost.[49] A full-length ADAMTS13 variant with an artificially introduced *N*-glycan and with these characteristics was recently reported by us.[127] Despite the current lack of in vivo data, rhADAMTS13 'bio-betters' like these could possibly be used with some anticipated advantages for the reduction of the burden of care (Figure 3).[128,129]

HOW TO FURTHER DECREASE THE BURDEN OF CARE IN TTP?

In one recent study, the inception of caplacizumab in the current SOC allowed for a significant reduction of deaths and volumes of plasma.[87] The high costs of such a regimen make it urgent for the field to reduce the burden of care. One obvious way to achieve this is through a steep reduction on the PEX regimen, e.g. a simple stoppage of PEX as soon as clinical responses and recovery ensue.[130] Plasma volumes involved in PEX have been a concern due to the risks associated with the procedure and the high plasma volumes necessary.[131] In addition, PEX is a cumbersome and expensive procedure, with complex logistics, and is not always readily available. In line with these statements, recent preliminary reports showed that it is possible to manage some patients without any PEX or plasma therapy at all, based on caplacizumab administration and immunosuppression.[130,132] In a series of case reports, six patients who experienced seven iTTP episodes and managed with such regimen recovered at least 10% of ADAMTS13 activity; all had clinical responses with improvement of platelet counts and lactate dehydrogenase (LDH) values.[132] Consequently, and although PEX still remains a cornerstone in the management of iTTP at the acute phase, PEX-free regimens should become feasible in the future, especially with the perspective of the introduction of rhADAMTS13 as a new player in the field.[122]

A replacement of therapeutic elements by other less expensive but equivalent alternatives is another way to further reduce direct costs: a biosimilar of rituximab has been reported to be equivalent in performance, with significant cost benefits.[133] Rituximab can also be adapted for subcutaneous use with similar performances in iTTP, yet reducing nursing workload, treatment time, and improving patient's satisfaction.[134]

LIFE WITH TTP: OUTCOMES OF TTP SURVIVORS

Improving relevant clinical outcomes for rare-disease patients and addressing patient concerns is coming into focus.[135,136] iTTP is known to be followed by several sequelae in the central nervous system[137] with chronic fatigue, headache, cognitive impairment, reduced work productivity, depression, anxiety,[136–139] post-traumatic stress disorder[140] and a lower QoL.[136,138,141] Current treatments do not prevent these
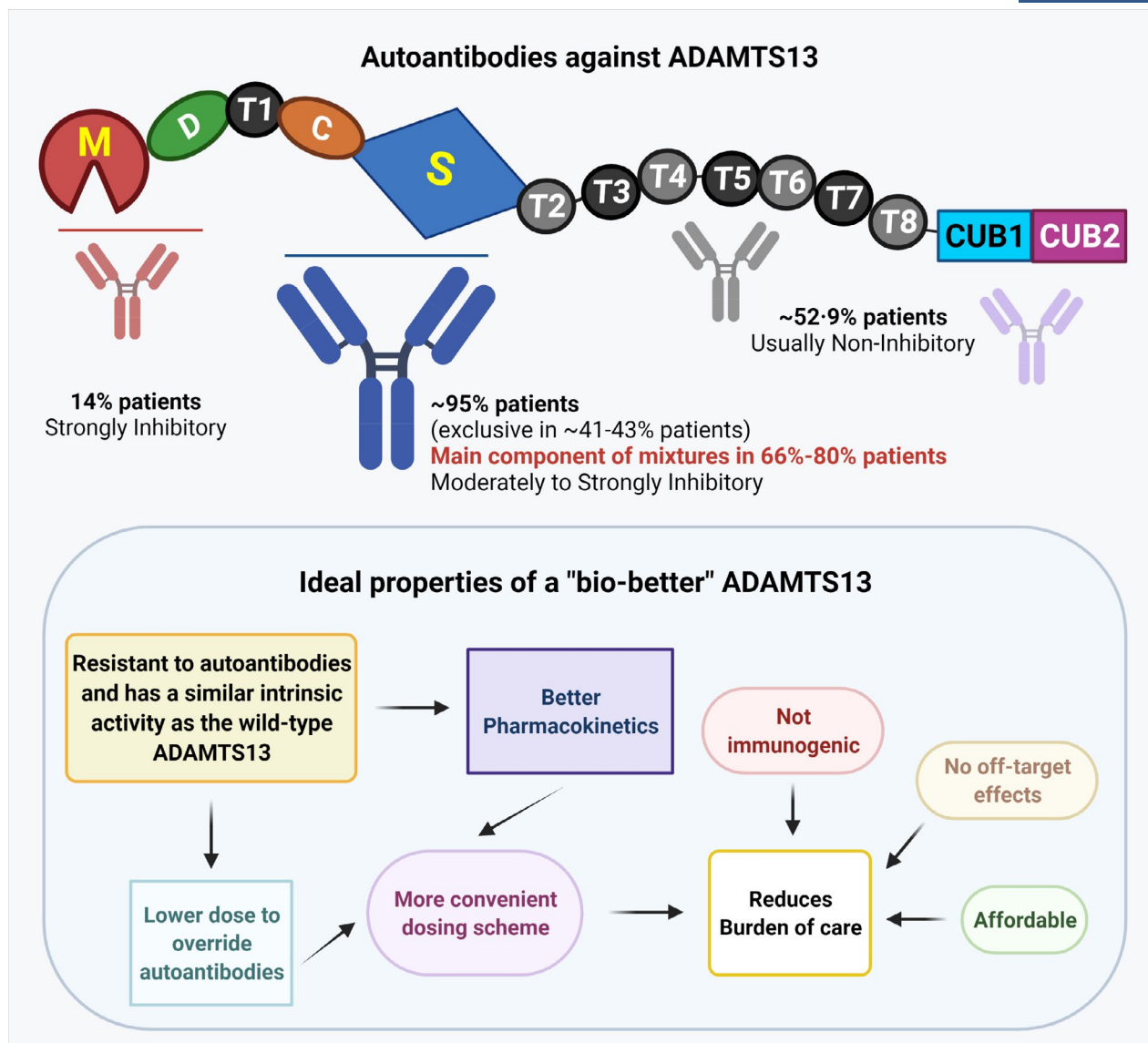
FIGURE 3 The nature of polyclonal autoantibody mixtures in Immune-mediated Thrombotic Thrombocytopenic Purpura (iTTP) patients and ideal characteristics of a 'bio-better' ADAMTS13. The domain structure of ADAMTS13 in single letter and number codes is shown. From left to right: M, metalloprotease; D, disintegrin; T1, thrombospondin (TSP) repeat 1; C, Cys-rich; S, spacer; T2–T8, TSP repeats 2–8; CUB-1 and CUB-2, complement subcomponent C1r/C1s, embryonic sea urchin protein Uegf, bone morphogenetic protein 1 domain. The general characteristics of patients' autoantibody mixtures are shown, based on compiled data shown in the supplementary data of reference [49]. Below, the ideal characteristics of a 'bio-better' ADAMTS13 are indicated with perspective of the anticipated advantages it should be able to offer over the wild-type rhADAMTS13. Several of these advantages are, in theory, linked. Notwithstanding, the wild-type rhADAMTS13 already promises to offer a significant reduction in the burden of care in iTTP and cTTP.[122] Figure created with BioRender.com

long-term outcomes, yet these are the ones patients complain about the most, although concern profiles are slightly different between cTTP and iTTP.[142] So far, the mechanisms behind the cognitive impairment observed are not yet fully defined, but likely involve ADAMTS13.[143] Microinfarcts and invisible lesions, and silent brain infarcts and other mechanisms are known to cause vascular-impairment dementia.[144] In the case of TTP patients, abnormal MRI scans are associated with neurological involvement at presentation and are predictive of long-term cognitive impairment.[145] These aspects raise the question of the target ADAMTS13 activity to be maintained after an acute TTP event, and may propel in

the future a revision of the current pre-emptive strategies as well as clinical follow-up and therapeutic evaluation according to underlying cardiovascular risk factors. Similar data were recently reported for cTTP patients.[115,118–121]

THE IMPORTANCE OF PATIENT EMPOWERMENT

Specific strategies for further patient empowerment need to be set. A recent questionnaire study submitted to 120 TTP patients revealed that two-thirds had a low to intermediate

literacy on their own condition, which is normally associated with older age and lower education levels.[146] Importantly, among the whole population studied, 39% of patients did not understand that PEX is mandatory in the acute phase, almost half of them do not consider being at risk of relapse, and 30% of women did not know that pregnancy increases the risk of relapse. Only one-third correctly replied what to do in case of a suspected relapse.[146] These findings show that there is a clear need for patients to better understand their disease (typically using non-technical language) and the importance of medical follow-up. Thereby, every aspect of long-term follow-up including prevention of relapses, pregnancy planning, contraception, identification and management of neurologic sequelae and cardiovascular risk factors must be addressed.

One effective tool for further patient empowerment is encouraging patients and family members to attend TTP support groups. Meeting other patients and exchanging their experiences together with specialists and researchers brings several benefits to both the patients' follow-up and learning, but also directing new research questions.[147]

THE TARGETS ON THE ROAD – PERSPECTIVES ABOUT THE FUTURE IN TTP

The field of TTP is experiencing several changes at a fast pace with exciting forthcoming challenges:

1. In the years to come, rhADAMTS13 should arise in the therapeutic landscape to bring further changes and reshape the current standards.[122] For iTTP, the strategy of overriding autoantibodies with the wild-type rhADAMTS13[123–125] allows for speculations on a 'bio-better' rhADAMTS13 that would be resistant against a large fraction of most patients' autoantibody mixtures (Figure 3).[49,126,128] We recently reported a full-length ADAMTS13 variant with an artificially introduced *N*-glycan bearing some of the *in vitro* characteristics of this idealized rhADAMTS13 'bio-better'.[127,129] Although further studies are still required before drawing more definite conclusions, the current scientific evidence is encouraging.

2. Raising the bar in the elderly is a current goal, since age does widen the risk for premature death of iTTP patients.[108] Caplacizumab may not prevent thromboembolic events as efficiently in this subpopulation, for which the use of adequate anti-platelet agents may further improve outcomes.[87]

3. It is necessary to gain more knowledge on the general cognitive deficits TTP patients develop, their mechanisms and how to prevent them. In this regard, caplacizumab and rhADAMTS13 hold a rationale; however there is yet lack of data in this field.[122] The cardiovascular risk factors these patients display must be aggressively controlled to prevent further damage, reduce comorbidities and improve outcomes in light of ADAMTS13 activity.[108,121]

In iTTP, ELISA-based detection of open-conformation ADAMTS13 may become helpful for a differential diagnosis, because it is a hallmark in acute-stage iTTP patients and reverts upon remission or rituximab treatment.[148,149] Importantly, this may become a useful predictive biomarker for imminent relapses.[149,150]

4. As a more long-term perspective, chimaeric antigen receptor (CAR)-T cells for the treatment of autoimmune diseases have attracted much attention. This approach could potentially be useful for treating more definitely the immune component of iTTP by clonally deleting anti-ADAMTS13-specific B-cells.[151]

5. Another strategy that holds promise is the use of gene therapy. In the case of TTP, several approaches have borne fruit in preclinical models: liposomal mRNA treatments,[152] gene transfer systems based on viruses,[153,154] in modified haematopoietic cells,[155] as well as direct hydrodynamic uptake of a sleeping-beauty transposon system carrying the *ADAMTS13* gene[156] have all been successfully applied in animal models. They can be used with any ADAMTS13 variant of choice.[152,154] A novel TTP model in zebrafish has recently been reported and may allow further understanding of the pathophysiology and discovery of novel treatments.[157]

After almost one century, TTP survival has now become the norm, and management is becoming simpler. However, the complex consequences of long-term TTP are still being unravelled and knowledge gaps remain that require attention. Studies are ongoing specifically to address these issues, and should shed light on these problems over the upcoming years. In the near future, the treatment landscape will likely see further exciting changes that hold much promise in answering part of the patients' unmet needs and complaints. Added to immunosuppression and caplacizumab, it will be exciting to see how the rhADAMTS13 will hold against the underlying immune response, how its regimen will be established, and how it will further reshape the current standards of practice.

CONFLICT OF INTERESTS

Nuno A. G. Graça and Jan Voorberg are inventors of a patent application regarding autoantibody-resistant ADAMTS13 variants. Karen Vanhoorelbeke is a member of the advisory board of Shire-Takeda and Ablynx-Sanofi. Agnès Veyradier is a member of the French advisory boards for Sanofi, Takeda, and Roche-Chugai. Paul Coppo was a member of advisory boards for and received speaker fees from Sanofi, Alexion, Octapharma, and Takeda. Nicolas Béranger and Bérangère S. Joly declare no conflicts of interest.

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