Developments in the use of plasma exchange and adjunctive therapies to treat immune-mediated thrombotic thrombocytopenic purpura

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Abstract

Introduction: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a life-threatening disease characterized by a severe functional deficit in the von-Willebrand cleaving protease ADAMTS13, due to autoantibody production. The once-dismal prognosis of the disease has been changed by the discovery of the dramatic efficiency of therapeutic plasma exchange (TPE).

Areas covered: This review focuses on the history and recent developments in the use of TPE for iTTP with a special emphasis on the consequences for TPE practice of the recent introduction of new highly effective immunosuppressive strategies and anti-von Willebrand factor therapies.

Expert opinion: Although TPE still represents the cornerstone, emergency treatment of iTTP, their duration, and associated cost and complications could be dramatically reduced in the next future by the systematic addition of early immunosuppression using corticosteroids and rituximab as well as an anti-von Willebrand factor therapy with caplacizumab.

Key words: ADAMTS13, caplacizumab, Plasma exchange, plasmapheresis, rituximab, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, von Willebrand factor

Article highlights:

- By supplying the deficient enzyme ADAMST13, therapeutic plasma exchange (TPE) still represents the cornerstone therapy of immune-mediated thrombotic thrombocytopenic purpura (iTTP).

- TPE at 1.0 to 1.5X estimated plasma volume should be emergently initiated when the clinical suspicion of iTTP is high and pursued until platelet count recovers.

- TPE in combination with immunosuppression with corticosteroids and B cell depletion with rituximab along with caplacizumab should become the standard of care to treat iTTP in the next future.

- Such combination is associated with a reduced need for TPE that now can be abruptly stopped after platelets recovery.

- The current development of a recombinant ADAMTS13 enzyme gives a glimpse into an attractive fully targeted strategy devoid of TPE for the next future of iTTP treatment.

List of abbreviations:

TTP: thrombotic thrombocytopenic purpura

vWF: von Willebrand factor

ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 repeats, 13th member

LDH: Lactate dehydrogenase

Ig: Immunoglobulin

cTTP: congenital TTP

iTTP: immune-mediated TTP

TPE: Therapeutic plasma exchange

EPV: estimated plasma volume

rhADAMTS13: recombinant human ADAMTS13

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a specific nosologic entity belonging to the group of thrombotic microangiopathies. TTP distinguishes itself among other thrombotic microangiopathies by its specific pathophysiology involving a severe functional deficit (activity < 10%) in the von Willebrand factor (vWF) cleaving protease, namely a disintegrin and metalloprotease with thrombospondin type 1 repeats, 13th member (ADAMTS13) **(table 1)**. This deficiency leads to the accumulation of ultralarge vWF multimers in the microcirculation, where maximal shear stress induces a change in vWF conformation, exposing the A1 domain and promoting platelet adhesion via glycoprotein Ibα. The subsequent formation of microthrombi leads to microvessels occlusion and promotes ischemic organ damage [1]. During TTP, the brain, the heart, and the digestive tract are particularly targeted, but virtually all organs might be affected. Accordingly, the clinical spectrum of TTP is associated with neurologic symptoms (60 to 80% of all TTP cases)[2–4], ranging from mild confusion to status epilepticus and/or coma ; cardiovascular symptoms (40 to 60%)[2,5], ranging from asymptomatic increases of cardiac troponin and electrocardiographic changes to refractory cardiac arrest; and digestive tract symptoms such as diarrhea and/or abdominal pain (35%)[2–4]. Unlike atypical hemolytic uremic syndrome, another thrombotic microangiopathy with distinct pathogenesis, renal involvement in TTP is usually mild (10 to 60%). Additionally, fever is not uncommon (10% to 50%)[2–4] and clinical onset might be preceded by flu-like symptoms. Microthrombi formation results in constant and severe consumptive thrombocytopenia (usually < 30G/L)[2–4], complicated by hemorrhagic symptoms (from purpura to intracranial hemorrhage); and in fragmentation of red blood cells, resulting in anemia with schistocytes

(microangiopathic hemolytic anemia). Finally, serum lactate dehydrogenase (LDH) elevation reflects both hemolysis and tissue damage and represents a central marker to assess disease activity and response to therapy [6,7].

TTP has a prevalence of about 10 persons out of a million and is two to three times more prevalent in women [2,3,8,9]. Two forms of the disease might be individualized according to the cause of ADAMTS13 activity deficiency, either inherited or acquired. In a few cases (less than 5% of all TTP cases), ADAMTS13 deficiency is congenital, in relation with biallelic mutations of the *ADAMTS13* gene, and referred as congenital TTP (cTTP), formerly known as Upshaw-Schulman syndrome, such situation being more frequently diagnosticated during childhood but not an uncommon diagnosis when TTP arises during pregnancy (24% to 66% of pregnancy-associated TTP cases) [8-10]. In the remaining cases, ADAMTS13 deficiency is acquired, most frequently related to anti-ADAMTS13 polyclonal antibodies, of the immunoglobulin (Ig) G isotype (and exceptionally IgA or IgM), responsible for ADAMTS13 inhibition. This situation is referred as immune-mediated TTP (iTTP), formerly known as Moschcowitz syndrome. Detection of autoantibodies targeting ADAMTS13 is the key element to distinguish iTTP from cTTP. However, such antibodies may not be detected in up to 22% of iTTP cases [3]; in this case, the restoration of a detectable ADAMTS13 activity following the acute episode confirms the diagnosis of acquired TTP. Conversely, the absence of anti-ADAMTS13 autoantibodies and the persistence of an undetectable ADAMTS13 activity during remission are the hallmarks of cTTP; in this situation, the identification of biallelic mutations within *ADAMTS13* gene (either homozygous or compound heterozygous) confirms the diagnosis. In addition to female sex, black ethnicity, obesity and HLA-DRB1*11 are predisposing factors for iTTP. Besides, the clinical flare is usually

triggered by one or several precipitating factors such as infection, sterile inflammation, and/or pregnancy, such conditions being associated with an increase in vWF production. In about half of the cases, iTTP is associated with a particular condition, such as autoimmune disease (mostly systemic lupus erythematosus or Sjögren syndrome) [13], a recent HIV infection [14], or pregnancy [3], and defines secondary iTTP. Finally, cTTP and iTTP are prone to relapse, and recurrence of a severe ADAMTS13 deficiency exposes patients to a new episode of TTP; for this reason, a long-term follow-up of patients with TTP is mandatory.

Nowadays, cTTP is efficiently managed by ADAMTS13 supplementation through plasma infusion, whereas iTTP requires a more intensive therapeutic regimen because of the ongoing autoimmune process. Once almost always fatal, the prognosis of iTTP has been changed by the discovery of the dramatic efficiency of therapeutic plasma exchange (TPE) which still represents the emergency treatment of patients having a confirmed or even suspected iTTP. This narrative review focuses on TPE for the treatment of iTTP and aims at summarizing their historical role, recent developments and future in the management of this life-threatening disease.

2. History and rationale of TPE in iTTP

It is noteworthy that the first mention of a transfusion technique efficacy in TTP can be found in the first report of the disease [15,16]. After the description of a 16-year-old girl suffering from fatal TTP, Moschcowitz mentioned four other cases similar to his, seen by Max Lederer. In contrast to his case, these four patients were treated by transfusion of red blood cells and recovered. These observations were published later, and although they most closely resemble auto-immune or

infectious hemolytic anemia, the idea that some hemolytic pathologies could be treated by transfusion techniques had taken root [17,18]. The following years were sparse with rare observations of TTP and even rarer reports of treatment using a transfusion technique. At that time, the disease was almost always fatal despite treatment by various combination of vitamins, adrenocorticotropin, corticosteroids, azathioprine, nitrogen mustard, antiplatelet agents such as dipyridamole or aspirin, heparin, streptokinase and/or splenectomy [19]. In 1959, Rubinstein reported the success of exchange transfusion in the cure of an 11-year-old girl suffering from TTP [20]. Transfusion techniques gained a renewed interest by the 1960s with the use of whole blood exchange transfusion rapidly followed by TPE [6,21]. These two techniques were at that time used empirically and quite indifferently. Retrospectively, two works have brought key findings to the understanding of the disease and to the choice of the best treatment. In 1977, Byrnes made the observation that only removal of whole blood followed by the infusion of a replacement fluid containing plasma (either whole blood or fresh plasma) was effective in the treatment of TTP with cerebral and pancreatic involvement in an 18-year-old pregnant woman [22]. Consequently, the patient completed therapy using plasma infusion and ultimately recovered. In 1981, Gottschall described a series of 11 patients with a clinical diagnosis of TTP and their evolution on treatment. Three groups of patients were individualized according to the type of blood products they received during exchanges therapies [23]. Three patients who received platelet-poor whole 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 [24]. Plasmatherapy, either by the sole infusion of fresh plasma or in the form of TPE gradually became the standard of care of TTP [25]. A randomized trial compared these two attitudes and concluded to the superiority of TPE over plasma infusion with regard to clinical response (Platelet count rise over 150 G/L and clinical improvement) [26]. Nevertheless, the larger volume of plasma and therefore, higher amounts of ADAMTS13 administered in the TPE group may have accounted for the clinical difference observed. It took a few more years for the deficient factor to be described as a protease cleaving vWF and preventing its accumulation in the form of proaggregant ultralarge multimers [27,28] and then for this protease to be isolated [29] and identified as ADAMTS13 [30,31]. Finally, the antibodies responsible for the inhibition of ADAMTS13 were identified as a cause for iTTP, whereas genetic deficiency as a result of biallelic mutations of *ADAMTS13* gene accounted for cTTP [30,32–34]. The rationale of TPE was then fully understood: First and foremost, TPE achieves ADAMTS13 supplementation without risking fluid overload and subsequent complications as well as removal of ultralarge vWF multimers and autoantibodies, although these last mechanisms might be of lesser importance in clinical efficacy.

Over the course of half a century, TPE gradually established itself as the standard of care of iTTP. Meanwhile, TTP mortality had fallen from 90 to less than 15% [4,19,25,26].

3. Practice of TPE in iTTP

Nowadays, iTTP represents a category I indication for TPE according to the American society for Apheresis, meaning a "disorder for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment" [35]. TPE should be initiated as soon as a presumptive diagnosis of iTTP is made, without waiting the result of ADAMTS13 activity measurement, because any delay is associated with worse prognosis [36]. If not immediately available, high-dose (25-30 mL/kg) plasma infusion should be given while waiting for TPE initiation [37,38]. However, such attitude rapidly exposes patients to fluid overload. Finally, due to the severity of initial presentation and/or to the density of care required by the iTTP patient, TPE is most often initiated within the intensive care unit.

3.1 Technical considerations

The term apheresis (from ancient Greek αφαιρειν, to separate or to take away) designs the procedure by which one specific fraction is separated from other components of the whole blood and extracted: blood cells (cytapheresis) or plasma (plasmapheresis). TPE consist of plasmapheresis where the extracted volume of plasma is discarded followed by the reinfusion of an equal volume of a replacement fluid, the nature of which (fresh frozen plasma or albumin) depending on the indication. The practice of TPE requires the use of a device capable of ensuring the extracorporeal separation of various components of the blood. Depending on the physical principle used, two categories of equipment can be described. Indeed, whole blood can be separated into its different constituents based on their specific gravity (centrifugation plasmapheresis) or size (membrane filtration

plasmapheresis). During membrane filtration plasmapheresis, diameter of membrane pores being about 0.5µm passes most of plasma constituents but not cellular elements, platelets, the smallest of them being in the order of 3µm. The two techniques are also distinguished by the necessary blood flow, filtration requiring higher flow rates (100 mL/min or higher) usually via central venous access, than centrifugation which only requires 50 to 80 mL/min blood flow, compatible with one (discontinuous flow) or two (continuous flow) peripheral vascular accesses. While centrifugation usually uses citrate for anticoagulation, filtration can be done with either heparin or regional citrate anticoagulation. There are several theoretical advantages associated with the use of regional citrate anticoagulation compared to heparin: higher efficacy due to difficulties in the adjustment of flow rate during the procedure and the absence of real-time monitoring of heparin [39], reduced risk of bleeding relying both on the absence of systemic anticoagulation and on the close monitoring of patient ionized calcium with systematic calcium supplementation, as well as no risk for heparin-induced thrombocytopenia [40]. Calcium supplementation could be of particular interest in iTTP patients with regards to the nature of the replacement fluid, exclusively consisting in fresh frozen plasma which also contains substantial amounts of citrate. In line with this assertion, the rate of systemic hypocalcemia is particularly high in this population and even higher when unfractionated heparin is chosen for anticoagulation compared with citrate [41]. Severe thrombocytopenia in iTTP exposes patient to a very high risk of life-threatening bleeding and therefore, some authors have reported their experience in the use of membrane filtration TPE without anticoagulation. Thus, in a population of critically ill patients undergoing TPE for various indications, the absence of anticoagulation didn’t lead to an

increased risk of filter clotting [41]. Nevertheless, this study might have been underpowered as larger cohort reported a three-fold increase in the frequency of such complication when only saline flushing was used as compared with unfractionated heparin [42]. However, membrane filtration plasmapheresis without anticoagulation for the first sessions of TPE should be an option to consider in some patients at high risk of bleeding or already experiencing such complication, especially when regional citrate anticoagulation is unavailable and/or contraindicated. Because citrate also chelates magnesium which contrary to calcium is not routinely supplemented and given the role of magnesium in endothelium homeostasis and platelet aggregation, the practice of TPE might have notable as-yet unexplored consequences in iTTP [43,44]. Therefore, systematic magnesium supplementation should be envisaged [40]. Additionally, one must know that the two techniques might be responsible for substantial loss of platelets and that excessive transmembrane pressure during membrane filtration TPE might lead to hemolysis. Moreover, depending on several factors such as volume of distribution and protein binding, a substantial removal of drugs during TPE might occur. This eventuality should be considered for each medication administered around TPE and if deemed necessary, posology and timing of drug administration should be adjusted.

Other selective or semi-selective purification techniques derived from plasmapheresis, such as immunoadsorption or double-filtration plasmapheresis (cascade plasmapheresis), have occasionally been used in the context of TPE, generally as a rescue therapy. Their benefit is uncertain since they are directed towards the elimination of autoantibodies rather than ADAMTS13 supplementation.

3.2 Dose intensity

Early studies suggested that the best therapeutic efficiency of TPE was reached when volume exchanged was at least 1.0X the estimated plasma volume (EPV) and frequency of TPE was once daily [7]. Such volume corresponds to 40 mL/kg in an average healthy individual but underestimate the plasma volume during anemia. For this reason, it is more accurate to use the following formula [45]:

$$\text{EPV (L)} = 0.065*\text{weight}\left(\text{kg}\right)*\left(1-\text{Hematocrit}\right)$$

Beyond 1.5X the EPV, the benefit of one TPE session is scarce, both in terms of ADAMTS13 supplementation (achieved concentration tending to the concentration in the fresh frozen plasma administered) as well as in the decrease in anti-ADAMST13 autoantibodies concentration (tending to zero in an exponential decay) and such attitude increases cost and duration of TPE [46]. However, reducing the time between two sessions by increasing the frequency of TPE to twice daily might have some interest, as time between two session allows for a plasmatic transfer of autoantibodies from extravascular spaces as well as “consumption” of the exogenous ADAMTS13 brought by the last TPE. Indeed, 10 to 40 percent of patients with iTTP are refractory to standard therapy associating once-daily TPE of 1.0X to 1.5X EPV and corticosteroids. Refractory iTTP encompasses failure to improve platelet count to double the initial value or platelet count < 50 G/L despite 4 days of treatment with persistence of elevated LDH level [47]. Due to the worse prognosis of exacerbating or refractory iTTP despite implementation of various treatments [48], twice-daily TPE was evaluated as a salvage therapy. In the two retrospective series published to date, twice-daily TPE resulted in survival rate of 82-95%, despite very severe initial presentation and/or unresponsiveness to initial therapy. However, due to concomitant administration of other salvage treatments

(rituximab, cyclophosphamide, cyclosporine A, vincristine and/or splenectomy), definite conclusion about the efficacy of twice-daily TPE is challenging [49,50].

3.3 Replacement fluid

To date, exogenous plasma is the only way to bring ADAMTS13 to the deficient, iTTP patient. Thus, there is a need to optimize the treatment using plasma as the sole replacement fluid for TPE. Several preparations of human plasma have been used, differing in the use and nature of a technology for pathogen reduction or inactivation. The physical or chemical processes to which plasma is subjected for security are likely to affect their qualitative content, especially regarding proteins involved in hemostasis. Indeed, ADAMTS13 activity seems to be preserved in all kind of plasma preparation [51,52]. In contrast, solvent detergent plasma appears to have a reduced content in high molecular weight vWF [52]. Several studies, mostly retrospective and small sized, have looked for clinical consequences of these disparities when each plasma was used as replacement fluid for iTTP. Overall, no differences in efficacy could be demonstrated between the historical quarantined fresh frozen plasma, solvent-detergent plasma or amotosalen-inactivated plasma [53–55]. However, the use of solvent-detergent or amotosalen-inactivated plasmas could be associated with a lower incidence of plasma-related adverse events [54,56]. Additionally, while remission rates did not differ, a faster platelet count recovery has been observed with the use of amotosalen-inactivated plasma [55][Garraud et al, in preparation]. The use of methylene-blue inactivated plasma has been discontinued in several countries due to allergy concerns. Moreover, such plasma seemed to be less effective when compared with fresh frozen plasma [57–59]. Finally, independently

of the securisation procedure, a cryoprecipitate-poor plasma can be obtained after slow thawing of a frozen plasma and removal of the formed sediment. The theoretical interest of this preparation, variously referred as cryoprecipitate-poor, cryosupernatant or cryodepleted plasma lies in its depletion in "cryofactors", including vWF [52]. Nevertheless, cryosupernatant plasma did not show clear superiority in any of the three trials that evaluated its use as a replacement fluid for TPE in iTTP [60–62]. Moreover, such preparation is not routinely available in all countries.

3.4 Complications

Although TPE is a relatively safe procedure when performed in stable patients, a higher rate of complication has been observed when TPE is performed for iTTP [63,64]. Several factors might account for such apparent discrepancy: first, the clinical picture of TTP is often more severe than other TPE indications, with patients frequently requiring admission in the intensive care unit; moreover, a high dose-intensity of TPE schedule is needed for iTTP; finally, iTTP requires plasma as the only replacement fluid during TPE which carries significantly more risks of adverse events than albumin. Each step of the TPE procedure, from catheter insertion to reinfusion of the replacement fluid can lead to adverse events. Thus, it is common to describe catheter-associated complications (pneumothorax, catheter-related bleeding, systemic or local catheter-related infection, catheter misplacement or dysfunction, thrombosis) and procedure-related complications (hypotension, arrhythmia, electrolyte disturbances, reactions to plasma, hemolysis, platelet loss, filter clotting). Notably, the frequency of major adverse events in patients with iTTP treated by TPE is decreasing, in accordance

with the decrease in TPE duration over time due to the progressive implementation of immunosuppression [65].

4. Adjunctive therapies

4.1 Immunosuppression

There is a strong rationale for the use of corticosteroids in iTTP because of its autoimmune nature and their empirical use spread very early. However, despite this pathophysiological rationale, their utilization lies on little evidence and their specific impact on iTTP outcome have been seldom evaluated. The demonstration of a dose-dependent effect argues for their use. Indeed, in a randomized trial comparing, in combination with TPE, high-dose methylprednisolone (10 mg/kg/day for 3 days, then 2.5 mg/kg/day) versus standard doses (1 mg/kg/day), the highest dosage demonstrated its superiority in terms of remission rate [66]. Additionally, corticosteroids have been shown to be more effective than cyclosporine A in suppressing anti-ADAMTS13 autoantibodies and in restoring ADAMTS13 activity [67]. Currently, most teams use standard doses of corticosteroids (1 to 1.5 mg/kg of prednisone equivalent) but higher doses could be used in the most severe patients, especially through pulses [68]. Of note, mostly due to their large volume of distribution, exceeding by many times the plasmatic volume, corticosteroids are barely removed during TPE (less than 1% of the administered dose) and therefore, their exact timing of administration regarding TPE schedule is of minor importance [69].

In addition to corticosteroids, rituximab, an anti-CD20 chimeric monoclonal antibody, was first used in patients who did not respond to initial therapy or

relapsed. In this population, rituximab administration was associated with a high rate of remission (82-100%) and prevented relapses that were less frequent and occurred later [70]. These encouraging results prompted the evaluation of rituximab as part of the first line therapy of iTTP in an open-label trial [71]. In this study, patients received rituximab 375 mg/m^2 starting within 3 days of admission for iTTP for up to 8 doses, along with corticosteroids and TPE. Patients treated by rituximab achieved complete response in 92.5% of the cases and had fewer relapse than historical controls (10 vs 52.5%, p=0.0011). Another study compared patients who received frontline rituximab before or after the third day of admission and showed that early (≤ 3 days) administration of rituximab was associated with a shorter time to remission (12 vs 20 days, p<0.001), a reduced number of TPE sessions (16 vs 24, p=0.03) as well as a reduced length of stay in the hospital (median 16 vs 23 days, p=0.01), compared with late administration [72]. Unlike corticoids, rituximab is substantially removed during TPE, and drops of 65%-77% in serum concentrations of rituximab were reported post-TPE [73]. This characteristic justifies its administration just after a session of TPE and motivated the evaluation of more intense therapeutics regimens. However, kinetics of B cell depletion were similar to what can be observed in other autoimmune disease treated without TPE and with standard rituximab dosage, suggesting that the total volume of rituximab (vascular and extravascular) remains sufficient and that even lower dosages might be adequate. It is likely that, unlike the malignant diseases for which it was the primary indication, rituximab does not need to be administered in such a high dose to treat iTTP. Thus, other administration schedules are currently being evaluated (NCT01554514). Others anti-CD20 antibodies such as ofatumumab have also been utilized in the management of iTTP. Because none of them have been evaluated in

comparison to rituximab, their place is limited to the treatment of patients who have had severe adverse reactions to rituximab infusion, especially if human anti-chimeric antibodies to rituximab are found [74]. Nevertheless, it should be known that cross-reactions may occur [75].

Other therapeutics have been used as salvage therapies in case of refractory iTTP, including cyclophosphamide, vincristine, cyclosporine A, mycophenolate mofetil, bortezomib or splenectomy (for a detailed review, see [76]). The rationale behind these therapies lies in optimizing the immunosuppressive regimen to stop the production of autoantibodies, either by directly targeting plasma cells, or by targeting accessory immune cells such as helper T cells. None of these strategies has been prospectively evaluated; consequently, none of these should be used before rituximab. In refractory iTTP, following effective B cell depletion, cyclophosphamide and/or splenectomy could be proposed as the next step of intensification [77]. The use of anti-plasma cell agents such as bortezomib appears promising but deserves further investigation as current evidence is limited to case reports and small series [78].

4.2 Anti-vWF therapy

A better understanding of the pathophysiological mechanisms of the disease as well as the development of therapeutic antibody engineering has allowed in recent years the development of drugs targeting the interaction between vWF multimers and platelets. Caplacizumab is one of these molecules and the only one to have reached the clinical stage successfully. Caplacizumab is a divalent nanobody targeting the A1 domain of vWF and thus blocking its interaction with platelets. In an animal model of iTTP, caplacizumab administration was able to

suppress vWF activity and was associated with resolution of hematologic manifestations of iTTP [79]. In humans, two trials have evaluated caplacizumab frontline in iTTP in association with standard treatment [80,81]. In the recent phase 3 trial, HERCULES, patients were randomized to receive caplacizumab (10 mg intravenously before the first TPE, followed by 10 mg subcutaneously daily) or placebo during TPE and for 30-days thereafter [81]. In this trial, patient treated with caplacizumab demonstrated a shorter time to first platelet recovery (median 2.69 vs 2.88 days, p=0.01) as well as a lower incidence of a composite outcome including TTP recurrence, TTP-related death or occurrence of a major thromboembolic event (12% vs 49%, p<0.001), as compared to placebo. Additionally, caplacizumab allowed a reduction in health care resource utilization, as exemplified by a reduced TPE duration (median 5.8 vs 9.4 days), and a shortening in the intensive care unit (median 3.4 vs 9.7) and in the total hospital (median 9.9 vs 14.4 days) length of stay. Importantly, caplacizumab treatment appeared to be safe, with side effect mostly consisting of minor mucocutaneous bleeding. Thus, caplacizumab provides the once-missing bridge to prevent early death while waiting for sustained restauration of ADAMTS13 activity by the immunosuppressive regimen. Given these impressive results, caplacizumab has been recently approved for the treatment of iTTP in conjunction with TPE and immunosuppression by both the European Medicines Agency in Europe (September 2018) and the Food and Drug Agency in the United States (February 2019). A Phase IIIb is currently ongoing to assess long term results of caplacizumab therapy in patients enrolled in the HERCULES trial (NCT02878603).

4.3 Other therapies

Antiplatelets agents such as aspirin and dipyridamole have been historically used in TTP to prevent platelet rich thrombi formation with inconsistent results [82,83]. Due to their non-specific mechanism of action, and now that caplacizumab should be used broadly, their use seems no longer justified.

N-acetylcysteine, by its ability to break disulfide bridges and thus to reduce the size of vWF multimers has raised some enthusiasm from the results of a fundamental work [84]. Nevertheless, these hopes have been disappointed by the inefficacy of N-acetylcysteine when used in a curative situation in pre-clinical models of cTTP and iTTP [85]. A pilot study is currently ongoing to determine the usefulness of frontline N-acetylcysteine in iTTP treatment (NCT01808521).

5.Conclusion

TPE gradually imposed itself, from an empirical life-saving therapy to the standard of care of iTTP. However, TPE does no longer represent the only treatment of iTTP as the therapeutic armamentarium has been enriched in recent years with the emergence of efficient therapeutics targeting the specific pathophysiological mechanisms of the disease.

6. Expert opinion

The aforementioned developments should associate and define a new standard of care for iTTP management, relying on three axes: emergency ADAMTS13 supplementation by means of TPE, inhibition of platelet-vWF interaction and subsequent microthrombi formation using caplacizumab, and immunosuppression with corticosteroids and frontline rituximab (**figure 1**). The systematic combination of these treatments could virtually eliminate the risk of

death in the acute phase of an iTTP flare as suggested by the results of the most recent trials. However, in order for these impressive results to be translated into real life and the risk of early death completely eliminated, this therapeutic strategy should be implemented as soon as possible after the onset of symptoms. This supposes that efforts must be focused on early identification of the disease and avoidance of misdiagnosis, especially toward autoimmune cytopenia [86]. Secondly, and because ADAMTS13 activity dosage usually takes several days to be performed, a probabilistic approach to initiate therapy must be adopted to avoid any unacceptable delay. Thus, patients with a high probability of having a TTP should receive the appropriate treatment pending confirmation or reversal of the diagnosis. For this purpose, several scores have been developed such as the French score and PLASMIC score [87,88]. Patients with a high probability of iTTP according to these scores should receive without delay the full therapeutic regimen (**Figure 1**) [89]. The measurement of ADAMTS13 activity occupies a central place both in the confirmation of the diagnosis and in the assessment of treatment response. Therefore, sequential dosages should be ordered, starting on a weekly basis after platelet count recovery. While treatment with TPE can be stopped as soon as platelet count recovers (platelets > 150 G/L for two days), caplacizumab and corticosteroids should be continued until restoration of ADAMTS13 activity at a level acknowledged to protect patients from the disease (ADAMTS13 activity> 20%), in order to prevent exacerbations or early relapse. Because of its effect on relapse prevention, patients should receive a full course of rituximab. Once clinical remission is achieved, i.e., a response persisting at least 30 days after the last TPE, a regular long term follow up with serial monitoring of ADAMTS13 activity should be initiated. The identification of a decreased ADAMTS13 activity < 20% during follow-

up should prompt to administer rituximab, in order to prevent relapse that occurs in 74% in case of persistently decreased ADAMTS13 activity [90,91]. The role of twice-daily TPE as well as other salvage therapies including cyclophosphamide, vincristine, cyclosporine A, anti-plasma cell agents or splenectomy in the management of refractory iTTP will need to be redefined in the light of the use of caplacizumab; it is likely that their need should become scarcer. This new standard of care should be associated with a global reduction in TPE use for iTTP both in the acute phase, with the reduction in the length between initiation of therapy and response as well as for relapse which could be prevented in most cases.

The next step in the success story of targeted therapies for iTTP should logically be the administration of recombinant human (rh)ADAMTS13, instead of whole plasma, to achieve the replenishment of ADAMTS13. In an animal model of cTTP, administration of rhADAMTS13 in *adamts13* knockout mice subjected to TTP flare by vWF infusion successfully prevented or reverted the disease's characteristic manifestations including thrombocytopenia, anemia and LDH elevation [92]. These promising pre-clinical data prompted the evaluation of a rhADAMTS13 in the clinical setting of cTTP in a phase I trial [93]. In this study, administration of increasing doses of rhADAMTS13 led to a dose-dependent increase in ADAMTS13-mediated vWF cleavage products and was well tolerated. rhADAMTS13 is now being evaluated in cTTP in a phase 3 trial (NCT03393975). Interesting data were also obtained from animal models of iTTP. In a rat model of iTTP, the early administration of rADAMTS13 allowed an overriding of anti-ADAMTS13 inhibitory antibodies with restoration of ADAMTS13 activity and degradation of ultralarge vWF multimers translating into an improvement in hematological parameters as well as a in a reduction in microthrombi formation in brain and kidney [94]. Additionally, it

has been shown that rhADAMTS13 was able to restore vWF-cleaving activity when added to the plasma of iTTP patients with inhibitory autoantibodies, with a linear correlation between autoantibodies titer and required rhADAMTS13 [95]. Furthermore, amino acid substitution in the spacer domain of ADAMTS13 results in several gain of function variants, some of which being resistant to inhibition by autoantibodies from patients with iTTP and therefore could be of interest in the specific context of iTTP [96]. There is no doubt that the evaluation of a rhADAMTS13 will be the next major step in the search for the optimal iTTP therapeutic strategy. The success of such an approach would allow a fully-targeted, plasma-free therapeutic strategy, devoid of TPE related complications.

Now that the therapeutic armamentarium allows remission in almost all cases of the once-fatal iTTP, research should gradually shift to other horizons and two issues emerge particularly. First, the optimization of the follow-up once remission is achieved. It has already been shown that regular, lifetime monitoring of ADAMTS13 activity with preemptive administration of rituximab can prevent the occurrence of a relapse [90,91]. It is now necessary to define the ideal monitoring strategy as well as the schedule of rituximab administration and the best strategy to manage patients for whom the administration of rituximab would not be sufficient to restore detectable ADAMTS13 activity. Finally, it is known for years that iTTP survivors have altered quality of life and are at greatest risk for several comorbidities including post-traumatic stress disorder, hypertension, obesity, cognitive decline, major depression, autoimmune diseases, as well as for premature death [97–99]. The rate of depressive symptoms appears to be particularly high, concerning 20 to 80% of all iTTP survivors [98,100–102]. Several hypotheses have been raised to explain these findings. Among them, consequences

of microvascular damages during the first episode of iTTP or subsequent relapses as well as subclinical cerebrovascular and cardiovascular damages in case of reduced ADAMTS13 activity despite clinical remission deserve attention as they can be seen as modifiable factors. Future work should focus on whether newest therapeutic regimens as well as an optimized follow-up and pre-emptive strategy can reduce the incidence of these late complications.

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Figures and tables

	Immune-mediated TTP	Congenital TTP	Infection-induced HUS	Atypical HUS	Secondary HUS*
Typical population	Adults	Children and pregnant women	Children >> adults	Children and adults	Children and adults
Predominant manifestations	Neurologic symptoms (lethargy, confusion, epilepsy, stroke, coma) Cardiac symptoms (troponin elevation, overt myocardial infarction, hypotension, shock, cardiac arrest) No or mild renal insufficiency Severe thrombocytopenia (usually < 30 G/L)	Typical flares similar to immune-mediated TTP. Additionally, non-overt manifestations might occur such as recurrent episodes of headache, abdominal pain, hemolysis and/or thrombocytopenia [10] Clinical features are usually easily controlled with plasma infusion (TPE not required)	Renal insufficiency Diarrhea Rarely, symptoms related to an invasive pneumococcal infection (bacteremia, meningitis and/or pneumonia)	Renal insufficiency Hypertension Mild thrombocytopenia (typically > 30 G/L)	Variable, depending on the associated condition; frequent renal insufficiency
ADAMTS13 activity	Very low (< 10%)	Very low (< 10%)	Normal of mildly reduced	Normal of mildly reduced	Normal of mildly reduced
Etiology	Anti-ADAMTS13 antibodies	Mutations of *ADAMTS13* gene	Infection from Shiga-toxin producing *Escherichia Coli* Infection from *Streptococcus pneumoniae*	Alternative-complement pathway dysregulation - Inherited: Mutations of *CFH, CFI, C3, CFB, THBD, MCP* - Acquired: anti-CFH antibodies DGKε deficiency Cobalamine C deficiency Plasminogen deficiency	Bone marrow or solid-organ transplantation Malignancy and/or chemotherapy Autoimmune disease Drugs Malignant hypertension Pregnancy HIV

Table 1. Immune-mediated TTP and differential diagnosis of the TMA spectrum. TMA is a generic term used to describe a pathological process of intraluminal thrombotic occlusion of the microcirculation resulting in thrombocytopenia, microangiopathic hemolytic anemia and organ dysfunctions of various severities. TMA syndromes thus encompass several heterogenous nosologic entities relying on distinct pathophysiological mechanisms. TTP and HUS were formerly confounded due to partially overlapping clinical and biological presentation. The discovery of a severe functional ADAMTS13 deficiency as a hallmark of TTP along with the progressive dismemberment of HUS pathophysiological mechanisms explain why the unprecise and incorrect term “TTP-HUS” should be abandoned. In the absence of an obvious cause and because of the negative prognostic impact of any delay in treatment initiation, the diagnosis of immune-mediated TTP should be evoked and the specific treatment started if the clinical probability is high. Several scores such

as the French Score or PLASMIC score have been developed for this purpose [87,88]. In addition to the classic features of TMA (thrombocytopenia and hemolytic anemia with schistocytes), these scores are based on the severity of thrombocytopenia and the mild nature of renal impairment. *Also termed secondary TMA. TTP: Thrombotic thrombocytopenic purpura, HUS: hemolytic and uremic syndrome, TPE: Therapeutic plasma exchange, CFH: Complement factor H, CFI: Complement factor I, C3: Component 3, CFB: Complement factor B, THBD: Thrombomodulin, MCP: Membrane cofactor protein, DGKε: Diacylglycerol kinase ε, HIV: Human immunodeficiency virus, TMA: Thrombotic microangiopathy.

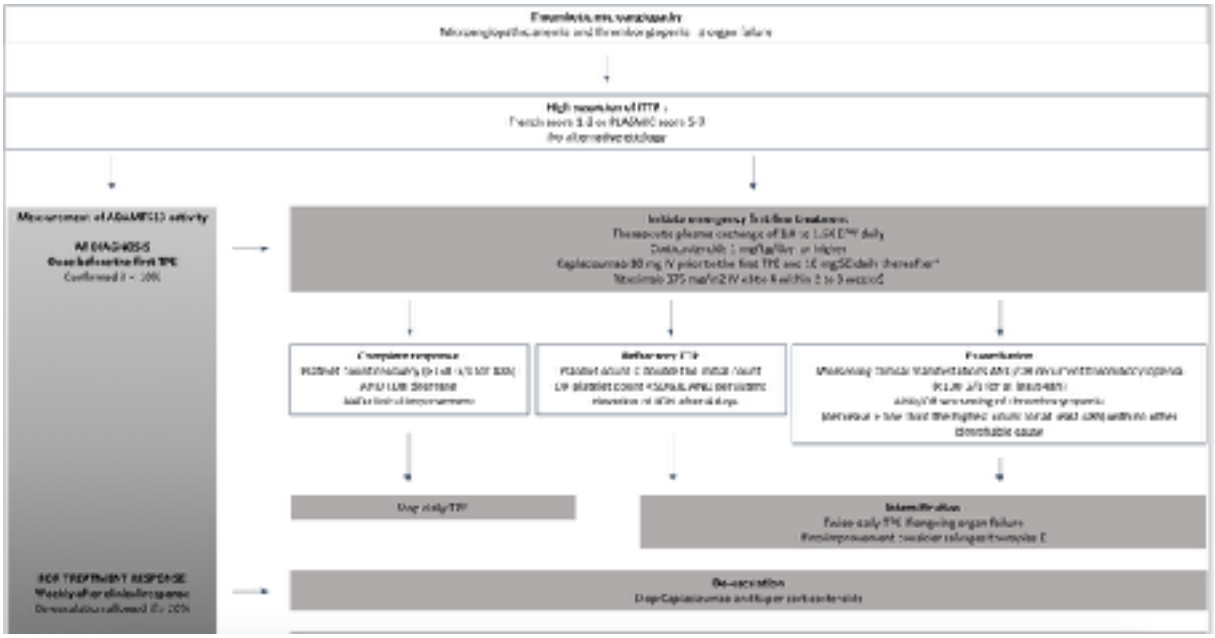

Figure 1. Approach to the diagnosis and management of patients with iTTP (adapted from [89]).

* Caplacizumab is listed as 10 mg single-dose vials in Europe and 11 mg single-dose vials in the United States. However, each single-dose vial contains the same amount of caplacizumab, which appears to be closer to 11 mg according to a dose recovery study. $ Other rituximab regimens are currently under investigation £ including cyclophosphamide, vincristine, cyclosporine A, bortezomib and/or splenectomy. °After restoration of a normal ADAMTS13 activity (i.e. > 50%), a progressive spacing of measurements is allowed, starting on a 3-month basis. iTTP: Immune-mediated thrombotic thrombocytopenic purpura, EPV: Estimated plasma volume, IV: Intravenous, SC: Subcutaneous, LDH: Lactate dehydrogenase.