Developments in thrombotic thrombocytopenic purpura and ADAMTS13

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Actualités dans le purpura thrombotique thrombocytopénique et ADAMTS13

ADAMTS13, von Willebrand factor, thrombotic thrombocytopenic purpura, haemostasis, thrombotic microangiopathy

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a specific form of thrombotic microangiopathy arising from a severe functional deficiency of ADAMTS13, the specific Von Willebrand factor (VWF) cleaving protease. This defect leads to the accumulation of hyperadhesive VWF high-molecular-weight multimers and to the spontaneous formation of microthrombi in the microcirculation, accompanied by peripheral thrombocytopenia and mechanical haemolytic anaemia. TTP is mainly an acquired disease, most often autoimmune (iTTP) but can also be inherited (cTTP) when deleterious bi-allelic mutations are found in the ADAMTS13 gene (Upshaw-Schulman syndrome). TTP is a relapsing-remitting disease requiring long-term follow-up. TTP is either idiopathic (50%) or associated with a physiological or pathological context such as pregnancy, autoimmune disease, infection, neoplasia or transplantation. TTP is a disease, the diagnosis and management of which have changed dramatically over the last 30 years, mainly due to breakthroughs in the understanding of the relationship between VWF and ADAMTS13. TTP is a therapeutic emergency and can be detected by clinical prediction scores (French Score, PLASMIC Score). However, formal diagnosis relies on the measurement of ADAMTS13 activity, which is <10 IU/dL. Biological confirmation should not delay treatment, particularly the initiation of plasma replacement therapy to provide exogenous ADAMTS13, which is the cornerstone of treatment in the acute phase of TTP. Immunomodulatory therapies, such as rituximab (monoclonal antibody to CD20) are also recommended for iTTP. Finally, caplacizumab, a monoclonal antibody targeting the A1 domain of VWF, has recently joined the therapeutic arsenal after very satisfactory results in terms of reduction of morbidity and mortality according to international clinical trials. A recombinant ADAMTS13 is currently being evaluated with promising preliminary results. Innovative tools to explore anti-ADAMTS13 autoimmunity are emerging: ADAMTS13 conformation and anti-ADAMTS13 antibody epitope-mapping. These tools may allow the identification of subgroups of patients of varying severity and consequently lead to their therapeutic stratification.

Résumé

Le purpura thrombotique thrombocytopénique (PTT) est une forme particulière de microangiopathie thrombotique résultant d'un déficit fonctionnel sévère en ADAMTS13 (pour a disintegrin and metalloprotease with thrombospondin type I repeats-13), la protéase spécifique de clivage du facteur Willebrand (VWF). L'accumulation de multimères de haut poids moléculaire de VWF hyperadhésifs aux plaquettes conduit à la formation spontanée de microthrombi dans la microcirculation, accompagnée d'une thrombopénie périphérique et d'une anémie hémolytique mécanique. Le PTT est très majoritairement une maladie acquise, le plus souvent auto-immune (PTTi) mais peut également être congénital (PTTc) et lié à des mutations délétères bialléliques du gène ADAMTS13 (syndrome d'Upshaw-Schulman). Le PTT évolue par poussées entrecoupées de rémissions, avec un risque de rechute nécessitant un suivi au long cours. Le PTT est idiopathique dans 50 % des cas, mais il peut également compliquer des contextes physiologiques ou pathologiques (grossesse, maladie auto-immune, infection, néoplasie ou greffe). Le PTT est une pathologie dont le diagnostic et la prise en charge ont drastiquement changé au cours des 30 dernières années, principalement en raison de l'avancée des connaissances sur le couple VWF/ADAMTS13. La PTT est une urgence thérapeutique, et le diagnostic présomptif peut être posé par des scores de probabilité clinicobiologique (French Score, PLASMIC Score). Le diagnostic de certitude repose toutefois sur la mesure de l'activité d'ADAMTS13, attendue effondrée (< 10 %). La confirmation biologique ne doit en aucun cas retarder la prise en charge, en particulier l'instauration d'une plasmathérapie substitutive permettant l'apport d'ADAMTS13 exogène, pierre angulaire du traitement de la phase aiguë du PTT. Les traitements immunomodulateurs, notamment le rituximab (anticorps monoclonal anti-CD20), sont également indiqués dans le PTTi. Enfin, le caplacizumab, un nanocorps dirigé contre le domaine A1 du VWF, a récemment rejoint l'arsenal thérapeutique après des résultats très satisfaisants en termes de diminution de la morbimortalité, d'après les résultats d'essais cliniques internationaux. Une ADAMTS13 recombinante est actuellement en cours d'évaluation, avec des résultats préliminaires prometteurs. Des outils innovants d'exploration de l'auto-immunité anti-ADAMTS13 émergent: la conformation d'ADAMTS13 et la cartographie des anticorps anti-ADAMTS13. Ces outils pourraient permettre l'identification de sous-groupes de patients de sévérités variables et ainsi conduire à leur stratification thérapeutique.

Von Willebrand factor and ADAMTS13

Von Willebrand factor (VWF) is a multimeric glycoprotein synthesised by endothelial cells and megakaryocytes. VWF plays a major role in primary haemostasis and is essential for platelet adhesion to the sub-endothelium exposed by vascular breach as well as for the aggregation of platelets in the blood stream under high shear forces (microcirculation). The haemostatic power of VWF regarding platelets and the sub-endothelium is proportional to its degree of multimerisation [1].

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In 1996, the specific VWF cleavage protease, capable of regulating the distribution of VWF multimers, was partially purified from human plasma by two independent groups [2, 3]. In 2001, thanks to the genomic approach, this protease was identified as the 13th member of the family of ADAMTS proteases (for *a disintegrin and metalloprotease with thrombospondin type 1 repeats)*, and is, therefore, referred to as ADAMTS13 [4]. The ADAMTS13 gene is located on chromosome 9q34 and comprises 29 exons. ADAMTS13 is a single-stranded glycoprotein of 1,427 amino acids (190 kDa), synthesised in liver perisinusoidal stellate cells, endothelial cells and megakaryocytes. It is secreted into plasma at a concentration of about 1 mg/mL and has a plasma half-life of two to three days [5]. The mature protease consists of the following structural domains: a metalloprotease (M), disintegrin (D), thrombospondin type 1 (T1), cysteine-rich domain (C), *spacer* (S), seven thrombospondin type 1 domains (T2-T8) and two CUB domains (*Complement, sea Urchin EGF* and *Bone morphogenetic protein, corresponding to these* three proteins) [6].

The native conformation of ADAMTS13 is closed and maintained by an interaction between its *spacer domain* and its CUB domains, inhibiting the metalloprotease domain rendering it cryptic. The interaction between ADAMTS13 and its substrate, VWF, is specific. The T8-CUB2 domains of ADAMTS13 bind to the D4CK domains of VWF. Allosteric activation of ADAMTS13 allows exposure of its cryptic catalytic site (M) which can bind to the A2 domain of VWF in the presence of high intravascular shear forces or within an arterial thrombus, cleaving it at the Tyr1605-Met1606 peptide bridge [7] (*figure 1*).

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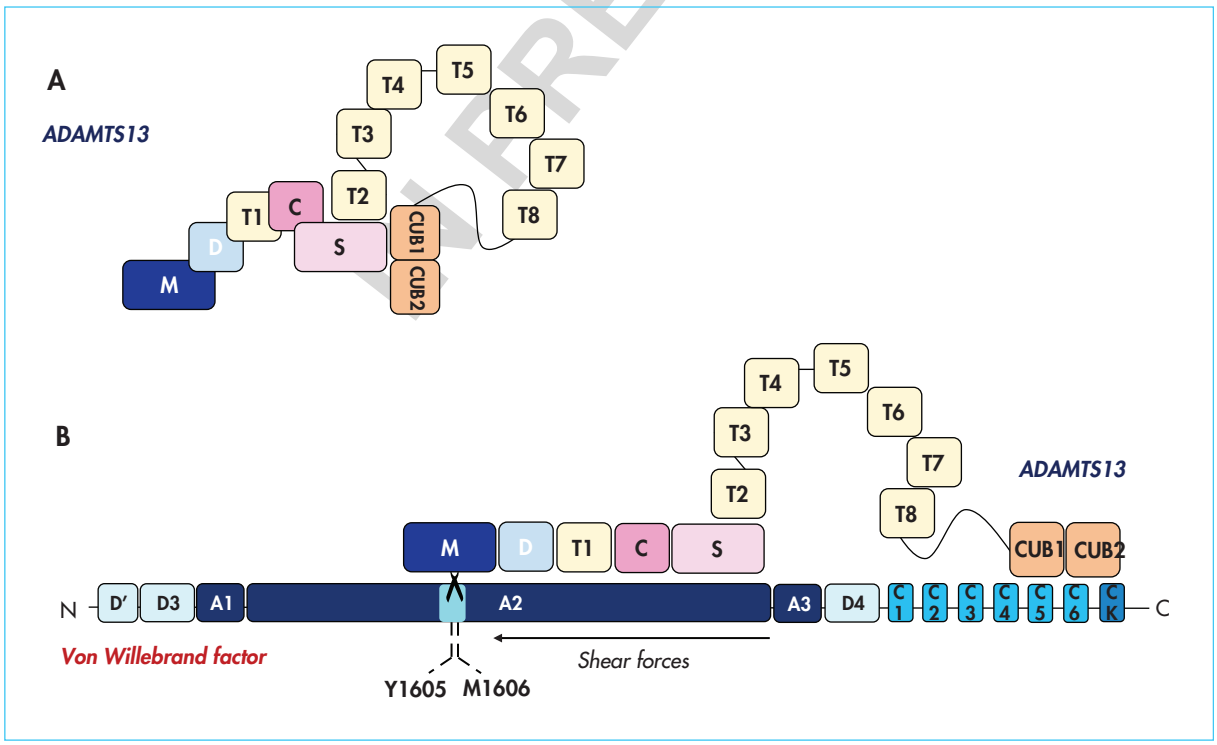
Figure 1



Interaction between Von Willebrand factor (VWF) and ADAMTS13. VWF is a mosaic protein composed of several domains: D1-D2-D'-D3-A1 A2-A3-D4-C1-C2-C3-C4-C5-C6-CK. ADAMTS13 is a single-stranded glycoprotein with the following structural domains: a metalloprotease (M), disintegrin (D), thrombospondin type 1 (T1), cysteine-rich domain (C), *spacer* (S), seven thrombospondin type 1 domains (T2-T8) and two CUB domains. ADAMTS13 adopts a closed conformation through an interaction between its *spacer domain* and its two CUB domains (A). Auto-inhibition at the level of the *spacer domain* and the two CUB domains can be overcome by the interaction between ADAMTS13 and its substrate, VWF (B).

Pathophysiology of thrombotic thrombocytopenic purpura

In 1924, Eli Moschcowitz described the first fatal case of thrombotic thrombocytopenic purpura (TTP) in a 16-year-old girl [8]. In 1982, Moake *et al.* reported the presence of platelet thrombi rich in very high-molecular-weight multimers of VWF in the microvessels of patients with TTP [9]. In 1998, after being purified from human plasma, the specific VWF cleavage protease was studied in patients with TTP [10, 11]. TTP is a specific form of thrombotic microangiopathy (TMA) and the interaction between VWF and ADAMTS13 is crucial in the pathophysiology of the disease. Severe functional deficiency of ADAMTS13 (activity < 10 IU/dL) is responsible for the accumulation of high-molecular-weight VWF multimers and spontaneous formation of microthrombi composed of VWF agglutinates and platelets, resulting in severe peripheral thrombocytopenia ($< 30 \times 10^9$/L) [10, 11]. The microthrombi obstruct the microcirculation, causing, on the one hand, mechanical haemolytic anaemia, with the appearance of schistocytes, and, on the other hand, tissue ischaemia of varying severity, defining the TMA syndrome [12]. Severe ADAMTS13 deficiency, pathognomonic for TTP, is [4, 13]:

– either acquired (aTTP) and mainly mediated by anti-ADAMTS13 autoantibodies (iTTP),
– or congenital (cTTP) and associated with the presence of biallelic mutations in the ADAMTS13 gene (autosomal recessive disease, Upshaw-Schulman syndrome).

Clinical presentation of thrombotic thrombocytopenic purpura

The clinical picture of a TTP flare-up can be extremely variable, but mainly involves signs related to anaemia and severe thrombocytopenia (asthenia, dyspnoea, mucocutaneous purpura, *etc.*), neurological involvement (60% of cases; headache, confusion, ischaemic stroke or seizure), and sometimes intestinal (35%), cardiac (25%) and renal (20%; proteinuria, haematuria) involvement (*figure 2*). TTP is a disease that progresses with unpredictable acute events interspersed with periods of remission of varying duration. The inaugural acute event of TTP is either idiopathic (50% of cases) or associated with a particular clinical context (50%; mainly infection and autoimmune disease, neoplasia, organ or haematopoietic stem cell transplant, *etc.*) (*Table 1*).

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Epidemiology of thrombotic thrombocytopenic purpura

TTP is a rare disease with an estimated incidence of 1.5 new cases per million people per year and a prevalence of 4–10 cases per million people [14]. There is a clear predominance of females in the acquired autoimmune form (sex ratio F/M = 2 to 3.5) [13, 14]. The first acute event of TTP occurs mainly in adulthood (90% of cases), but the diagnosis of TTP should also be made in childhood (10% of cases) so as not to delay specific treatment. The distribution of acquired and congenital forms differs according to the age of the first acute event (*figure 3*). In adults, aTTP accounts for 98% of all cases of TTP, and cTTP is reported in fewer than 2% of cases; it is revealed mainly in obstetrical settings [14, 15]. In children, aTTP and cTTP account for approximately 70% and 30% of cases, respectively [16, 17].

Diagnostic strategy of thrombotic thrombocytopenic purpura

In the event of suspected TMA syndrome, certain investigations, in particular, should be implemented based on the overall flowchart of investigation for ADAMTS13. The French Score [18] and the PLASMIC Score [19] are predictive of severe ADAMTS13 deficiency. These scores have been developed to assist in the presumptive diagnosis of TTP, allowing rapid initiation of treatment (plasma replacement therapy, *see below*), limiting the morbidity of this disease.

Table 1

Demographic, clinical and biological characteristics of the French thrombotic thrombocytopenic purpura cohort (based on Mariotte *et al.* [14]).

	Total (n = 772)	Idiopathic TTP (n = 378)	Non-idiopathic TTP (n = 394)	*p*
Age	43 (32–59)	42 (31–53)	45 (32–60)	< 0.0001
Women	525 (68 %)	257 (68 %)	268 (68 %)	0.75
Men	247 (32 %)	121 (32 %)	126 (32 %)	
Neurological impairment	471 (61 %)	249 (66 %)	221 (56 %)	0.011
Fever	309 (40 %)	140 (37 %)	169 (43 %)	0.072
Digestive disorders	270 (35 %)	144 (38 %)	126 (32 %)	0.043
Albuminemia (g/L)	77 (65–91)	77 (63–92)	75 (66–89)	0.052
Platelet count ($\times$ $^{109/L}$)	15 (9–30)	14 (9–22)	20 (9–39)	< 0.0001
Creatinine (mmol/L)	126 (87–204)	115 (84–163)	148 (89–250)	0.0006
LDH (U/mL)	1,596 (988–2,715)	1,707 (1,001–2,752)	1500 (885–2,703)	0.49
Anti-ADAMTS13 IgG positive (> 15 U/mL)	564 (73 %)	336 (89 %)	228 (58 %)	< 0.0001

Quantitative parameters are expressed as median and interquartile range and qualitative parameters as number and percentage. All tests were considered statistically significant for $p < 0.05$. A χ^2 test was performed to compare demographic and clinical variables; a Mann-Whitney test was performed to compare biological parameters.

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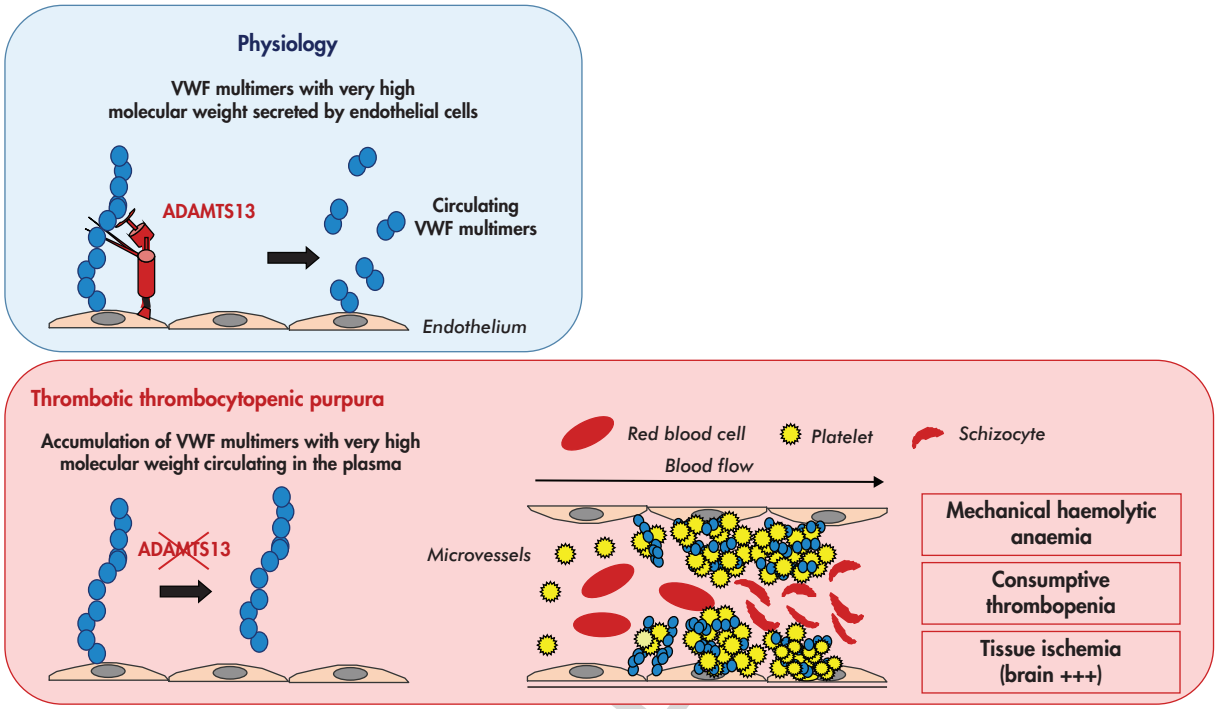
The measurement of ADAMTS13 activity, carried out on citrated plasma or serum, is a first-line examination to steer diagnosis in the event of any suspicion of TMA. Techniques for measuring ADAMTS13 activity have evolved considerably since 1998, alongside the understanding of the physiology of VWF/ADAMTS13 [20]. The principle of all methods for measuring ADAMTS13 activity is based on the degradation of an exogenous native VWF substrate *(full-length)* or a synthetic 73-amino-acid peptide (VWF73) by ADAMTS13 in the test plasma, followed by detection of the VWF degradation products by electrophoretic methods, IRMA (*immunoradiometric* assay) and CBA (*collagen binding* assay) (first-generation tests) [20], fluorometric (FRETS-VWF73, international reference method) and ELISA (enzyme-linked immunosorbent assay) tests [20] (second-generation tests) [21, 22], or chemiluminescence (third-generation test) [23].

This latest third-generation test is fully automated, adaptable to emergency situations, and has very good diagnostic and analytical performance. It is, however, expensive [24].

Severe deficiency of ADAMTS13 activity (<10 IU/dL) confirms the diagnosis of TTP [12]. Anti-ADAMTS13 immunoglobulin G (IgG) testing and titration is the second test that should be performed for severe functional ADAMTS13 deficiency. If anti-ADAMTS13 IgG is positive, the diagnosis of iTTP is retained. In the absence of anti-ADAMTS13 IgG, biological monitoring is recommended to make the diagnosis of aTTP retrospectively, in the presence of detectable ADAMTS13 activity in remission. In the absence of anti-ADAMTS13 IgG, and depending on the clinical context (newborn, child, obstetrical context, *etc.*), sequencing of the ADAMTS13 gene is proposed in order to search for the presence of biallelic mutations of this gene, supporting the diagnosis of cTTP *(figure 4)*.

FIGURE 2



Pathophysiology of thrombotic thrombocytopenic purpura. Severe functional deficiency of ADAMTS13 (activity < 10 IU/dL) results in a defect of Von Willebrand factor (VWF) proteolysis and accumulation of very high-molecular-weight, hyperadhesive VWF multimers and spontaneous platelet thrombi in the microcirculation. This causes consumptive thrombocytopenia, fragmentation of red blood cells on the surface of microthrombi (mechanical haemolytic anaemia, schistocytes, consumptive thrombocytopenia) and a defect in tissue perfusion (multivisceral ischaemia).

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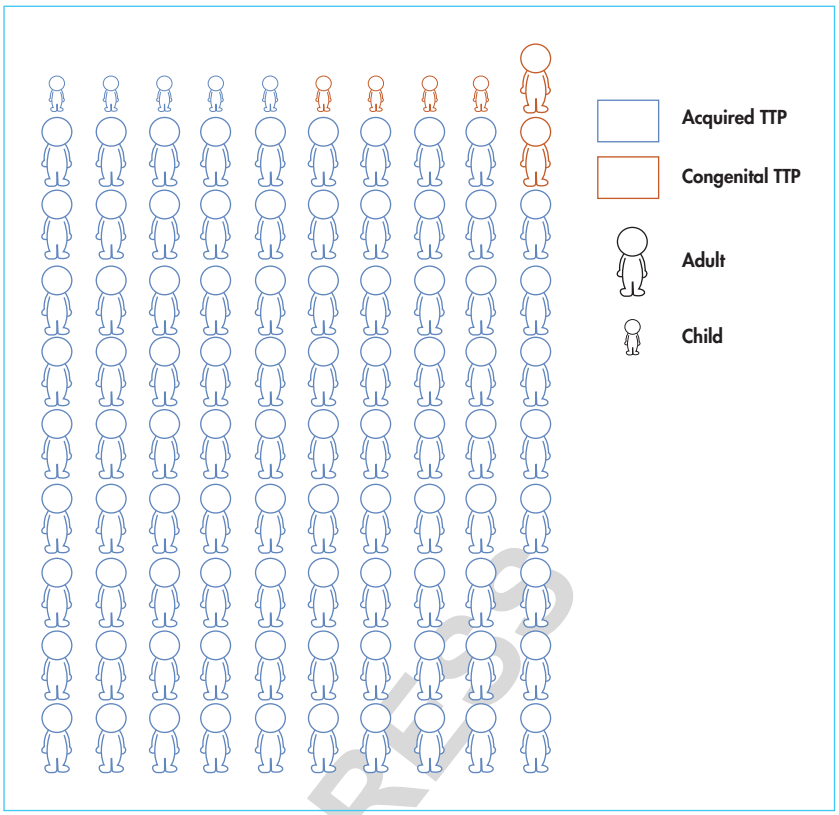
It should be noted that the time it takes to receive the ADAMTS13 results should not delay treatment. The sample for ADAMTS13 investigation must be taken before the implementation of plasma replacement therapy (exogenous contribution of ADAMTS13, *see below)*, and diagnostic confirmation of TTP can then be made retrospectively, within a few days.

Latest advances in the pathophysiology of thrombotic thrombocytopenic purpura

In iTTP, recent work has shown that there is a breakdown in immune tolerance resulting in the appearance of anti-ADAMTS13 autoantibodies responsible for a functional blockage or acceleration of ADAMTS13 clearance via the formation of immune complexes that are rapidly eliminated [11, 14]. Autoantibodies to ADAMTS13 are predominantly IgG, but IgM or IgA isotype antibodies have been described in 20% of patients. IgG autoantibodies are polyclonal but are predominantly directed against the spacer domain of ADAMTS13 corresponding to the binding site with the A2 domain of VWF (*figure 4*). Among the anti-ADAMTS13 IgG, the IgG4 subclass predominates, followed by IgG1, IgG2 and IgG3. The distinction of IgG isotypes and subclasses has prognostic value in the disease. The presence of IgA and/or IgG1 in the initial phase of TTP is associated with a poor prognosis, and a high level of IgG4 is thought to be associated with a high risk of relapse [13]. Several studies dedicated to mapping the spacer domain of ADAMTS13 in iTTP have shown that five positively charged residues (Arg568,

Figure 3



Distribution of 100 cases of thrombotic thrombocytopenic purpura (TTP) according to age at onset and mechanism of severe ADAMTS13 deficiency. The first attack of TTP can occur in adults (>90 of 100 cases) or, more rarely, in children. Severe functional ADAMTS13 deficiency can be acquired (>95 of 100 cases, mainly with anti-ADAMTS13 autoantibodies) or is rarely congenital (biallelic mutations of the ADAMTS13 *gene*).

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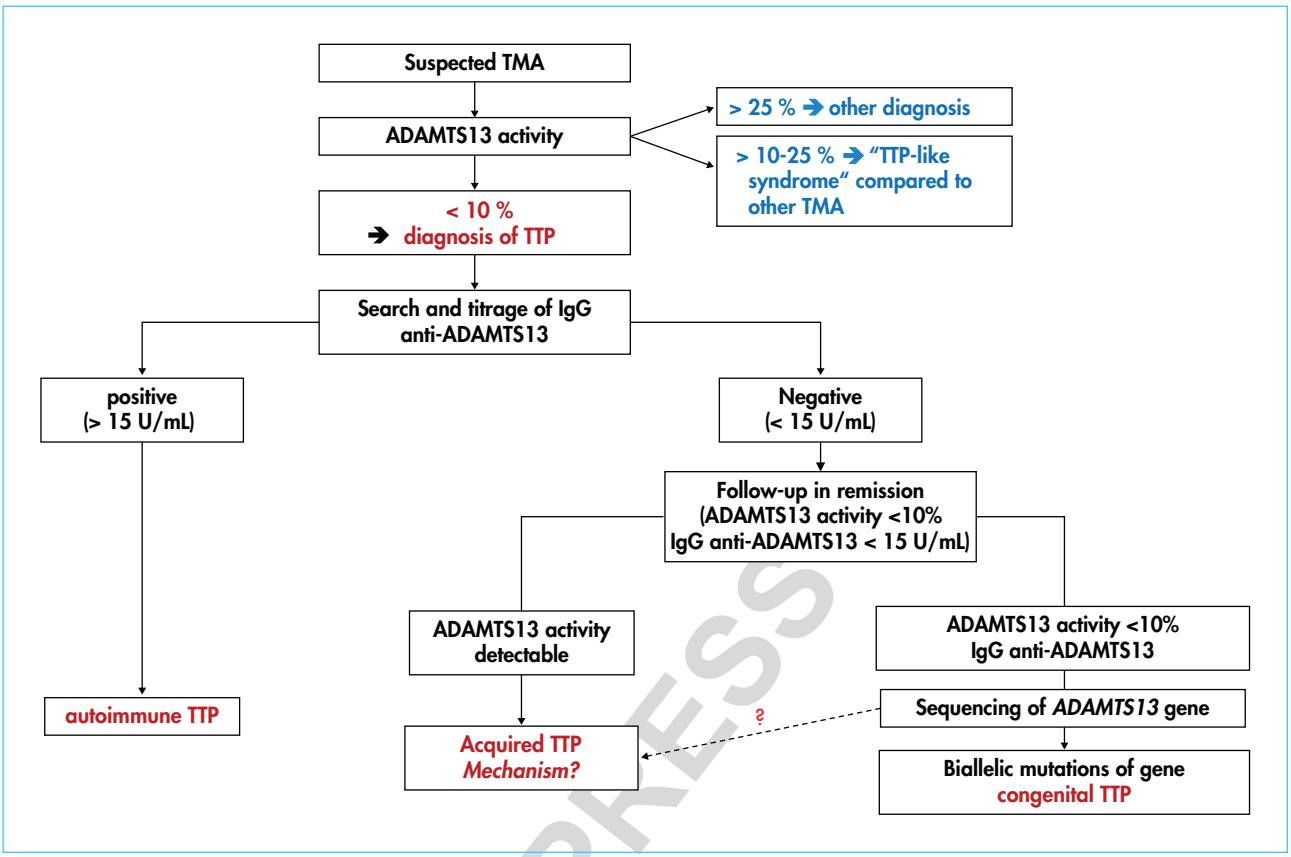
Arg660, Phe592, Tyr661, and Tyr665) constitute the major antigenic surface of anti-ADAMTS13 [7]. When the ADAMTS13 protease adopts a closed conformation, these residues are hidden by the CUB domains. In iTTP, ADAMTS13 adopts a specifically open conformation in the acute phase [25] allowing exposure of the cryptic domain of the spacer domain, which becomes the main target of anti-ADAMTS13 [26]. However, the mechanisms involved in the loss of autotolerance to ADAMTS13 are not well understood. There are predisposing factors for TTP (female, African or Caribbean patients, HLA DRB1*11) and triggering factors (pregnancy, infection and inflammation) [13].

In cTTP, nearly 200 distinct mutations in the ADAMTS13 gene have been described, including nucleotide substitutions (62%), nonsense mutations (12.5%), splicing mutations (8%), deletions or insertions (17.5%), located along the entire length of the gene, with no *hot-spot* mutations. Two mutations are highly represented: the c.4143_4144dupA duplication in exon 29 described in Central and Northern European families (prevalence: 0.04–0.33%) and the c.3178C > T substitution (p.Arg1060Trp) in exon 24, reported in adult-onset cTTP in the obstetrical setting (prevalence: 0.3–1 %). Several polymorphisms *of* ADAMTS13 can influence the penetrance of certain mutations (p.Arg7Trp, p.Gln448Glu, p. Pro618Ala, p.Ala732Val, p.Ala900Val, and p.Ala1033Thr). Correlations between phenotype and genotype are difficult to establish, given the high level of heterogeneity of ADAMTS13 [17].

Figure 4



Decision tree for the investigation of ADAMTS13. The measurement of ADAMTS13 activity in citrated plasma or serum is indicated as a first-line step for any suspicion of thrombotic microangiopathy (TMA) in the acute phase (a sensitive and specific parameter for the diagnosis of TTP), and in the biological follow-up of patients in remission (prognostic value for the risk of relapse). A severe functional ADAMTS13 deficiency (ADAMTS13 activity < 10 IU/dL) confirms the diagnosis of TTP. Anti-ADAMTS13 IgG is titrated when ADAMTS13 activity is severely deficient, revealing the presence of autoantibodies against the protease. In clinical remission, detectable ADAMTS13 activity points to an acquired form of TTP; undetectable ADAMTS13 activity and the absence of anti-ADAMTS13 IgG points to a possible congenital form of TTP.

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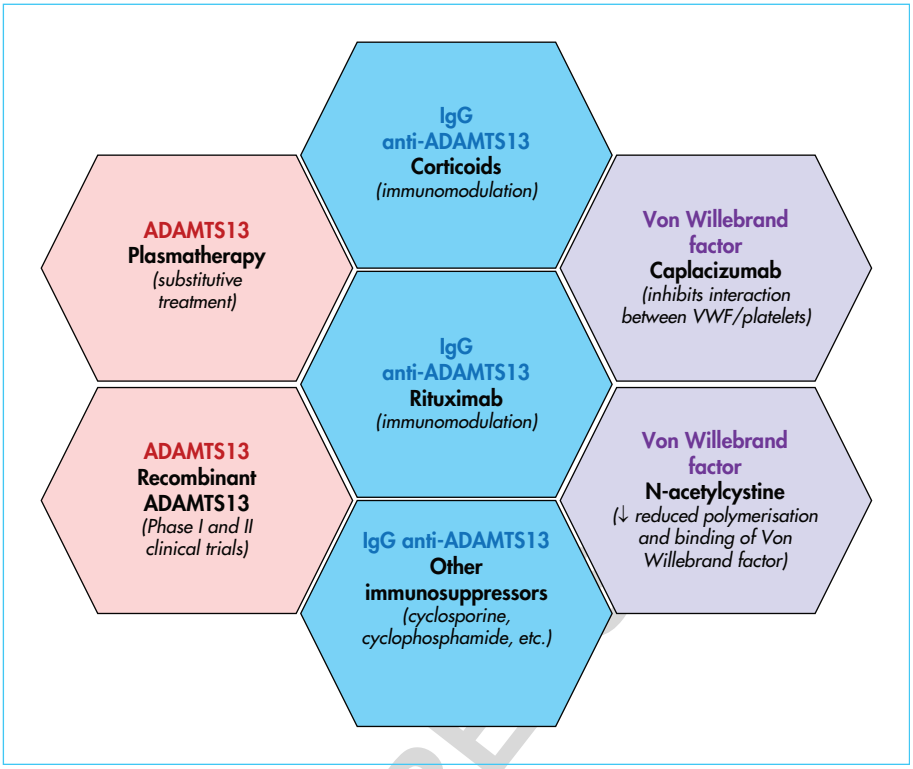
Therapeutic targets in the management of thrombotic thrombocytopenic purpura (*figure 5*)

The therapeutic treatment of the acute phase of TTP is an emergency. The frequency of ischaemic organ failure should lead to hospitalisation in an intensive care unit. First-line treatment is based on plasma replacement therapy (plasma exchange [PE] or, failing that, fresh frozen plasma [FFP] infusions). Several therapeutic targets have been described in TTP: ADAMTS13 protease, anti-ADAMTS13 autoantibodies (immunomodulators) and VWF (inhibition of VWF/platelet interaction) [27].

Plasma replacement therapy provides exogenous ADAMTS13 (cleavage of high-molecular-weight VWF multimers and saturation of anti-ADAMTS13 autoantibodies in iTTP). PE may decrease the concentration of anti-ADAMTS13 autoantibodies, although the actual benefit of this effect has never been demonstrated. It is the first-line treatment for all iTTP and cTTP acute phases. In cTTP, prophylactic plasma therapy is the only treatment option available (10 mL/kg), and the frequency of plasma infusions is guided by the chronicity of the disease. The immunomodulatory treatments used in iTTP eradicate anti-ADAMTS13 autoantibodies.

Figure 5



Therapeutic targets in thrombotic thrombocytopenic purpura (TTP). Therapeutic targets in TTP include the ADAMTS13 protease, anti-ADAMTS13 autoantibodies and the VWF/platelet axis. Plasma exchange, plasma infusion and recombinant ADAMTS13 provide an exogenous supply of ADAMTS13. Corticosteroids, rituximab (an anti-CD20 drug) and other immunosuppressive drugs can eliminate anti-ADAMTS13 autoantibodies. Finally, caplacizumab and N-acetylcysteine limit the formation of platelet-rich and Willebrand factor-rich microthrombi.

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Corticosteroids and rituximab (anti-CD20 monoclonal antibody) are currently used as first-line therapy in adults in the absence of contraindications, and always in combination with PE. Rituximab is not immediately effective (average delay of two weeks) and does not prevent early deaths, which most often occur within the first ten days of treatment [28]. Other immunosuppressive strategies (vincristine, cyclophosphamide and cyclosporine, or splenectomy) can be considered in refractory forms of iTTP but are used increasingly rarely since the use of caplacizumab. Caplacizumab is a bivalent humanised nanobody targeting the A1 domain of VWF and inhibiting its interaction with platelet GPIb. It is a molecule which received marketing authorisation in 2018 on the basis of the results of the two clinical trials, TITAN and HERCULES [29, 30]. Treatment with caplacizumab reduces time to normalisation of platelet count, mortality, exacerbations and early relapse of iTTP. The safety profile is very favourable, although some mucocutaneous bleeding, mostly minor or moderate, has been reported. A treatment regimen combining PE, caplacizumab and immunosuppression (corticosteroids and rituximab) prevents unfavourable outcomes in iTTP [31].

Another innovative therapy, recombinant ADAMTS13 (rADAMTS13), is emerging in the management of the disease. The results of the Phase I study of rADAMTS13 are encouraging and report good tolerance and efficacy of the treatment (decrease in high-molecular-weight VWF multimers, increase in platelet count and decrease in lactate dehydrogenases [LDH]) [32]. Two therapeutic trials dedicated to

rADAMTS13 are ongoing: a Phase III trial for cTTP (ClinicalTrials.gov, number NCT04683003) and a Phase II trial for aTTP (ClinicalTrials.gov, number NCT03922308).
N-acetylcysteine has mucolytic properties and may limit the polymerisation and binding of VWF multimers, however, due to its controversial efficacy - although minor compared to that of caplacizumab–it has recently been removed from the therapeutic arsenal [33].
It should be noted that transfusions of platelet concentrates are contraindicated in the absence of life-threatening bleeding symptoms, as they increase the formation of spontaneous platelet microthrombi.

Patient follow-up

International guidelines for the diagnosis and treatment of the inaugural phase of TTP have been developed under the auspices of the International Society of Thrombosis and Haemostasis (ISTH) [23, 34]. Long-term follow-up of patients is crucial to anticipate any relapses, to detect ischaemic organ sequelae or the emergence of another autoimmune disease (mainly connective diseases), and to support a planned or ongoing pregnancy. Relapse prevention is a major issue in iTTP. In the French trial conducted by the National Reference Centre for Thrombotic Microangiopathies (CNR-MAT), the follow-up of patients who presented with an episode of iTTP is well defined (referential of the French Haematology Society). Long-term follow-up of all patients is recommended every three months for the first year after the inaugural episode of iTTP. Follow-up visits can be spaced at six months in the second year and then at one year if there are no intercurrent events. Regular monitoring, usually quarterly, of ADAMTS13 biological activity is recommended to assess the risk of biological relapse and to anticipate any further clinical relapse. This follow-up should probably be offered for life, as late relapses can occur, sometimes several years after the initial episode. During follow-up, it is reported that ADAMTS13 activity < 10 IU/dL is associated with a cumulative incidence of relapse at seven years of 74%. Pre-emptive treatment with rituximab is therefore proposed to the patient in the event of severe deficiency in ADAMTS13 activity in order to prevent the risk of clinical relapse. Women of childbearing age must be supported to carry future pregnancies to term and should be supervised and monitored by multidisciplinary teams. The transition from childhood to adulthood is also an important stage in the lives of patients. Systemic disease, typically systemic lupus erythematosus or Sjögren's syndrome, may develop during follow-up and should be investigated.
In cTTP, regular clinical and biological monitoring, as well as testing for anti-ADAMTS13 alloimmunisation, is recommended in all patients receiving regular prophylactic plasma therapy.
Caplacizumab is indicated for the management of adult and adolescent patients (>12 years and >40 kg) with an episode of iTTP in conjunction with PE and immunosuppressive therapy. Treatment with caplacizumab for at least 30 days after discontinuation of daily PE is recommended, possibly extended to a maximum of 65 days. This treatment is initiated in hospital and continued when the patient returns home. A hospital-based clinical research programme, called CAPLAVIE, conducted in France under the aegis of the National Reference Centre for Thrombotic Microangiopathies, is designed to address whether a treatment duration of caplacizumab adapted to ADAMTS13 activity is as effective as a minimum treatment duration of 30 days.

Conclusion

Knowledge of the pathophysiology of TTP has evolved considerably over the last ten years. Investigation of the conformational change of ADAMTS13 in the acute

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phase of iTTP may be an early biomarker of relapse risk. The study of epitope mapping of anti-ADAMTS13 antibodies may predict the prognosis of the disease. A growing number of promising new therapies are now available (caplacizumab) or in clinical trials for TTP (rADAMTS13), and TTP is now entering the era of personalised medicine.

Conflicts of interest: AV, YB and PC are members of the French expert committee on TTP for Sanofi. PC is a member of the international committee of experts on TTP for Takeda.]

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