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Pathogenesis and treatment of acquired idiopathic thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic disease characterized by episodes of thrombocytopenia and microangiopathic hemolytic anemia due to disseminated microvascular thrombosis. TTP was first described in 1924 by Moschowitz as a disease presenting with a pentad of signs and symptoms (anemia, thrombocytopenia, fever, hemiparesis and hematuria).[1] Post-mortem examination showed widespread thrombi, mainly composed of platelets, in the terminal circulation of several organs. The description of von Willebrand factor (VWF) multimers of unusually large size in the plasma of patients with TTP represented a turning point for the understanding of the disease pathophysiology.[2,3] The presence in plasma of the highly platelet-adhesive unusually large multimers of VWF provided a plausible explanation for the platelet- and VWF-rich thrombi observed in the small vessels of patients with TTP. Studies in the late 1990s then independently demonstrated the severe deficiency of a specific VWF cleaving-protease in the plasma of patients with recurrent TTP.[4] This protease was identified as the thirteenth member of the ADAMTS (a disintegrin and metalloprotease with thrombospondins 1 repeats) family of metalloproteases, ADAMTS13.[5-7] Severe ADAMTS13 deficiency can be due to mutations in the *ADAMTS13* gene (congenital TTP)[8] or to anti-ADAMTS13 autoantibodies (autoimmune TTP).[9-11] The antibody-mediated severe deficiency of ADAMTS13 can be detected in most patients with idiopathic TTP (i.e. TTP occurring without associated clinical conditions/events), whereas its prevalence is much lower in the secondary forms of TTP (i.e. TTP associated with pregnancy, infections, autoimmune diseases and the use of drugs such as ticlopidine and clopidogrel).[12,13] It should also be mentioned that there are idiopathic cases of TTP with only slightly deficient or even normal ADAMTS13 levels at presentation, but these cases are not object of the present article in which idiopathic and autoantibody-mediated TTP are used as synonyms.

Epidemiology and clinical course of idiopathic thrombotic thrombocytopenic purpura

The incidence of idiopathic TTP is estimated to be 4.5/1 million person/years, being higher in blacks. The male to female ratio is 1:2, similarly to the ratio for other autoimmune diseases.[14] The acute prognosis of idiopathic, antibody-mediated TTP tends to be less severe, but the risk of recurrent disease is higher than that of secondary forms.[15,16] The overall mortality of TTP was higher than 90%, but has decreased to 8-30% after the introduction of plasma exchange, which is the treatment of choice of acute TTP episodes.[17-20] The lower mortality of patients with idiopathic TTP (21% *versus* 39% in the frame of the Oklahoma TTP registry[16]) is probably due to the higher response to plasma exchange of patients with autoantibodies and to the mortality related to associated conditions in secondary cases.[21] Up to 40% of patients with TTP develop recurrent episodes of the disease, with the risk of recurrences being higher in patients with severe ADAMTS13 deficiency and anti-ADAMTS13 autoantibodies during acute episodes.[15,16,22-24] The cumulative risk of recurrence at 7.5 years after the first episode in patients with ADAMTS13 activity below 10% at presentation was estimated to be 41%, 10 times that of patients with activity above 10% (4% risk at 7.5 years).[16] Persistence of ADAMTS13 deficiency and of autoantibodies during disease remission is also associated with increased risk of recurrence.[25,26]

Table 1. Features of novel drugs that could potentially be used in idiopathic thrombotic thrombocytopenic purpura along with plasma exchange.

Drug(s)	Pathogenic mechanism	Drug class	Mechanism of action	Stage of development
Rituximab. Other drugs under development	Production of anti-ADAMTS13 auto antibodies	Anti-CD20 antibodies	B-lymphocyte depletion	Available
Recombinant ADAMTS13	Impaired VWF cleavage	Recombinant replacement products	Replacement of deficient ADAMTS13	Pre-clinical development
Aptamer ARC1779 (Archemix Corp)	VWF binding to platelets and VWF-mediated thrombosis	VWF-platelet interaction inhibitors	Blockage of VWF-mediated platelet aggregation	Phase 2 clinical trial has been terminated since it was not possible to complete enrollment within a reasonable period of time
Nanobody ALX-0681 (Ablynx)	VWF binding to platelets and VWF-mediated thrombosis	VWF-platelet interaction inhibitors	Blockage of VWF-mediated platelet aggregation	Phase 2 clinical study under development

Characterization of anti-ADAMTS13 antibodies

Anti-ADAMTS13 autoantibodies have been the focus of several research efforts trying to characterize their immunoglobulin (Ig) subclass, specificity and mechanisms of action. Early studies distinguished two classes of anti-ADAMTS13 autoantibodies: inhibitory and non-inhibitory antibodies. Inhibitory antibodies are present in 50-90% and their mechanism of action is the inhibition of ADAMTS13-mediated proteolysis of VWF.[27] When non-inhibitory antibodies are also measured, anti-ADAMTS13 autoantibodies are detectable in 97-100% of patients.[27,28] The core binding site for VWF, located in the spacer domain of ADAMTS13 and consisting of amino acid residues Tyr572-Asn579 and Arg657-Gly666, represents the target site of the autoantibodies found in the plasma of several TTP patients.[29,30] The mechanism of action of non-inhibitory antibodies has been proposed to be opsonisation and enhanced clearance of ADAMTS13, but this has never been proven.[27,28] Studies on the class of anti-ADAMTS13 autoantibodies showed they are usually of IgG type, particularly IgG1 and IgG4 subtypes,[10,31] but in a few cases autoantibodies of IgA and/or IgM isotype were also found.[28,32] Most anti-ADAMTS13 IgG found in TTP patients were demonstrated to be directed against the spacer domain, but additional antibodies against other ADAMTS13 domains were also detected.[33,34] However, these studies were conducted in small cohorts of patients. In this issue of Haematologica, Zheng *et al.*[35] present the first study of antibody specificity on a relatively large group of patients with TTP, finding that, although almost all patients with IgG had antibodies directed against the N-terminal ADAMTS13 domains (Cys-rich through spacer), where the catalytic site of ADAMTS13 is located, up to 46% of TTP patients also had antibodies against C-terminal ADAMTS13 domains (TSP1-5 through CUB). Moreover, two patients had antibodies only against C-terminal domains of ADAMTS13, but not against N-terminal domains. These findings suggest a functional role of C-terminal domains of ADAMTS13 *in vivo*, also in light of the importance of these domains in the VWF-ADAMTS13 interaction under fluid shear stress. Importantly, Zheng *et al.*[35] correlated antibody specificity with clinical data, showing that patients with antibodies against ADAMTS13 C-terminal domains had lower platelet counts at presentation.

This is not the first time that anti-ADAMTS13 antibody features have been found to correlate with clinical outcomes in TTP. Patients with IgG subclasses 4 were found to be more likely to have disease recurrence than patients with IgG subclass 1.[31] Patients with high inhibitor titers were found to have worse acute-disease prognosis.[31] Consistently, patients with high levels of IgG (both inhibitory and non-inhibitory) were found to have a higher likelihood of developing cardiac involvement and, hence, a poorer prognosis in comparison to patients with low IgG levels.[36] All these findings indicate that different antibody features might be associated with clinical outcomes in TTP, but more comprehensive studies should be carried out before antibody characterization can be introduced into routine clinical practice of TTP. Moreover, other questions remain to be addressed.

Acquired TTP is surely an autoimmune disorder, at least in those patients with an autoantibody-mediated severe ADAMTS13 deficiency, but the mechanisms involved in the loss of tolerance of the immune system against ADAMTS13 are still unknown. The higher incidence of autoimmune idiopathic TTP in specific ethnic groups such as Afro-Caribbeans, as well as the report of idiopathic TTP in two monozygotic twins who both developed anti-ADAMTS13 antibodies,[37] strongly argue for a genetic predisposition even in the acquired form of the disease. In the last year two groups independently demonstrated an association between human leukocyte antigen (HLA) alleles and idiopathic TTP: HLA-DR and HLA-DQ typing suggests an underlying genetic risk for the development of TTP in Europeans.[38,39] As for the antibody characterization, confirmation of these results in larger groups of patients and in other ethnic groups are required prior to the introduction of HLA typing in the control of the disease.

Treatment and clinical trials in idiopathic thrombotic thrombocytopenic purpura

Plasma exchange remains the treatment of choice for acute episodes of TTP.[40] As mentioned, its introduction greatly reduced the disease mortality and it has been proven superior to plasma infusion.[18] Several different immunosuppressive drugs (corticosteroids, cyclosporine, azathioprine and, recently, rituximab) are added to plasma exchange by many centers, with the rationale that these

drugs help to stop antibody production in autoimmune cases, but their efficacy has never been confirmed by a large clinical trial. In addition to these treatments, novel drugs have been developed or are undergoing pre-clinical development for potential use in idiopathic TTP along with plasma exchange. These could tackle different aspects of TTP pathophysiology (Table 1). First, it is possible to reduce or abolish the production of anti-ADAMTS13 autoantibodies with anti-CD20 monoclonal antibodies that target B-lymphocytes (e.g. rituximab, but other more potent compounds are being developed).[41,42] Second, in principle, it could be possible to restore VWF cleavage in patients with severe ADAMTS13 deficiency with the use of recombinant ADAMTS13. Third, novel compounds that inhibit VWF binding to platelet glycoprotein Ib-alpha have been developed and could block VWF-mediated platelet activation. There is hope in the TTP community that these novel therapeutic strategies will be able to reduce the persistently high disease mortality. However, the availability of these new options entails a burden of new challenges for clinicians who have to deal with TTP patients, including uncertainties on the safety of the drugs in a delicate clinical setting such as that of a TTP patient during an acute episode and on the subgroup(s) of patients (idiopathic, secondary, TTP with prominent renal impairment, etc.) who could benefit from the treatment.

The efficacy and safety of these novel therapeutic strategies will need to be assessed in the frame of large clinical trials, a challenge for clinical scientists who work on this rare disease. The incidence of idiopathic TTP is such that any consortium willing to carry out a 3-year clinical trial involving roughly 100 patients would need to be able to cover a population of 66 million people (assuming an incidence of 4.5/1 million person/years). The choice of the clinical end-point is another challenge: mortality is approximately 20% which makes it a hardly targetable end-point. Surrogate end-points such as the incidence of stroke, renal failure, myocardial infarction, time to platelet recovery or clinical remission may be adequate for the definition of therapeutic efficacy but there are few data available from cohort studies that could inform the design of clinical trials employing these end-points. The picture is made even more complicated by the heterogeneity in the pathophysiological background of TTP. The inclusion in a TTP trial of secondary cases, patients with atypical hemolytic uremic syndrome, patients with a first TTP episode or recurrence may in principle conceal the effect of a treatment which is highly effective in a subgroup of TTP patients (e.g. only those with anti-ADAMTS13 autoantibodies). Recently, a phase 2, double-blind, placebo-controlled, clinical trial of intravenous ARC1779, an inhibitor of VWF binding to platelet glycoprotein Ib-α, was stopped due to slow recruitment (clinicaltrials.gov identification number NCT00726544). New trials are nonetheless being designed and carried out. These will be critical to the efforts of translating preclinical achievements into improvements in the care of this rare, but yet (and still) life-threatening thrombotic disease.

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Biological individuality and the new frontiers of immunological tolerance in hematopoietic stem cell transplantation

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Hematopoietic stem cell donors: rethinking traditional choices

From the time of the first successful experiences of allogeneic bone marrow transplantation,[1,2] and during the long previous history of failure,[3] it became clear that HLA-identity/compatibility between donor and recipient was an essential condition for the success of the transplant. Such compatibility is constantly found in homozygous twins (who also have identical minor histocompatibility antigens) and statistically in 25% of siblings. This HLA-compatibility was a necessary condition for the desired creation of a "biological chimera"; but transplant tolerance had to be promoted by lowering the recipient's immune response to prevent rejection, at least unless the patient was not seriously immunocompromised as, for example, in some cases of severe combined immunodeficiency. In particular, the use of total body irradiation since 1959, of cyclophosphamide since 1972, and of the combined use of both of these since 1974 are recognized as historical landmarks. Even after an HLA-compatible transplant, it was