Presse Med. 2012; 41: e101–e104

on line on
www.em-consulte.com/revue/lpm
www.sciencedirect.com

Thrombotic microangiopathies: From empiricism to targeted therapies

Paul Coppo[1]

UPMC université Paris 6, AP–HP, hôpital Saint-Antoine, service d'hématologie et de thérapie cellulaire, Paris, France

Available online: 7 February 2012

Correspondence:
Paul Coppo, Hôpital Saint-Antoine, département d'hématologie, 184, rue du Faubourg-Saint-Antoine, 75012 Paris, France.
paulcoppo@aol.com

In this issue

The diseases collectively termed thrombotic microangiopathies (TMAs) are various life-threatening disorders characterized by microangiopathic hemolytic anemia, peripheral thrombocytopenia and organ failure of variable severity caused by microvascular occlusion. In thrombotic thrombocytopenic purpura (TTP), the systemic microvascular aggregation of platelets causes ischemia in the brain, kidneys, heart and other organs. In hemolytic-uremic syndrome (HUS), fibrin-rich thrombi predominantly occlude the renal circulation. A TMA can also be typically observed in patients with the hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, disseminated cancer, or a human immunodeficiency virus infection and within the context of chemotherapy or transplantation.

For a long time, TMA remained a heterogeneous group of poorly differentiated diseases with obscure pathophysiologies. As a consequence, the treatment of TMA was based largely on empiricism and a few therapeutical trials. Fortunately, advances in recent years have delineated the molecular mechanisms of most of the TMA syndromes, including TTP, some atypical forms of HUS and the hemolysis, elevated liver enzymes, low platelet count syndrome and it is now clear that the TMA syndromes are caused by several distinct molecular defects.

In TTP, the identification of a severe deficiency in the von Willebrand factor cleaving protease ADAMTS13 by Tsai and Furlan in 1998 [1,2] provided an explanation for the accumulation of unusually large von Willebrand factor multimers in the plasma of patients with chronic relapsing TTP first reported by Moake in the 80 s [3,4]. ADAMTS13 deficiency could be due to mutations of the encoding gene or autoantibodies directed against various epitopes of the protein [5] that result in the functional inhibition of the enzyme and/or the formation of immune complexes that will be subsequently removed by phagocytes. The wide clinical and therapeutical perspectives opened in the field of TTP by the discovery of ADAMTS13 led clinicians and investigators involved in TTP (and TMA in general) to anxiously peruse the pages of medical and scientific journals for the adventures of this protein. Indeed, the accumulated knowledge about ADAMTS13 now allows us to understand that the effectiveness of plasma therapy, the cornerstone of treatment of TTP for more than three decades, is mainly due to its ability to supply large amounts of exogenous ADAMTS13. The mechanism of ADAMTS13 deficiency also provides an explanation for the different possible outcomes of the disease. Indeed, patients with a hereditary ADAMTS13

[1] French Reference Center for Thrombotic Microangiopathies.

doi: 10.1016/j.lpm.2011.10.023

deficiency usually experience multiple relapses that require prophylactic infusions of plasma according to the tolerance of the underlying disease. On the other hand, some patients with an acquired ADAMTS13 deficiency may experience a single episode of TTP, whereas others with anti-ADAMTS13 antibodies that persist in the circulation and lead to the continued inhibition of ADAMTS13 even after the achievement of remission may experience one or more relapses. Overall, 30% to 40% of patients with an acquired TTP can be considered to have a chronic relapsing disease, which can have a tremendous impact on their quality of life.

Almost simultaneously, a comparable pathophysiological breakthrough was achieved for atypical HUS. Mutations in proteins involved in the alternative complement pathway were identified in up to 70% of cases and could be associated with a specific prognosis. These mutations result in either a dysfunction of inhibitors, including factor H, factor I, membrane cofactor protein (MCP)/CD46 and thrombomodulin, or a gain of function of activators of the alternative complement pathway (factors B and C3). Anti-factor H antibodies were identified mostly in pediatric cases and were usually associated with the homozygous deletion of the complement factor H related gene. These abnormalities have a prognostic impact, with patients with factor H mutations having a 70% chance of eventually suffering from end-stage renal disease and an 80% chance of having a post-transplant relapse, whereas MCP/CD46 mutations lead to end-stage renal disease in 20 to 30% of cases in children and a low relapse rate after renal transplantation.

The novel concepts and disease mechanisms identified in the laboratory were rapidly and successfully transferred into the clinic for the benefit of patients and recent studies reporting on the use of monoclonal antibodies in the management of TTP and HUS provide convincing examples for the application of laboratory findings in translational medicine. Indeed, the B-cell depleting monoclonal antibody rituximab successfully treated refractory or relapsing acquired TTP in a large number of single reports and small patient series [6]. As a result, rituximab is gaining more and more popularity in the treatment of patients with acquired TTP who are experiencing a suboptimal response to standard plasma exchange-based treatment [7] and as a neo-adjuvant therapy along with therapeutic plasma exchange according to some groups [8]. Preliminary reports have emphasized the remarkable efficiency of eculizumab, the first humanized monoclonal antibody directed against the C5 component of complement, in the treatment of atypical HUS [9]. Indeed, the results of two international studies presented at the 2010 Congress of the American Society of Nephrology clearly indicated that eculizumab represents a breakthrough in the management of those patients [10,11]. Consequently, eculizumab should become the first-line treatment for this disease, and will no doubt profoundly impact the progression of the disease by preventing the evolution to end-stage renal disease and allowing dialyzed patients to have a successful kidney transplant. At the time of this issue is declared the end of the deadliest outbreak of shigatoxin-producing *Escherichia coli* Germany has ever recorded, with more than 4000 infected people, 50 deaths and more than 900 cases of HUS. This outbreak surprised the general public and public health officials, but it represented the opportunity to use eculizumab in more than 100 patients with a diagnosis of shigatoxin-associated HUS [12], while the experience of this antibody in this indication was so far limited to only three cases and published just some days after the outbreak started. The need to treat patients in emergency hampered to set up a rigorous controlled clinical trial and clinicians will have to consider multiple confounding factors; however, the results of this impromptu trial are of course awaited with a great interest.

From a perspective point of view, the development of other compounds based on pathophysiological findings is an area of intense therapeutical investigation. Among these, recombinant ADAMTS13 is obviously considered a promising therapy when available. In other situations, inhibitors of the platelet-von Willebrand factor interaction [13] may represent interesting possibilities as therapeutic agents for certain well-defined indications and require accurate evaluation in large clinical trials. In addition, the development of both compounds aimed at protecting damaged endothelium in microvessels and inhibitors of the polymerization of von Willebrand factor multimers [14] deserve evaluation as therapies.

Although it is disturbing to note that the diagnosis of TMA is still delayed in some patients, clinicians are becoming more and more aware about this diagnosis. Thus, it is likely that this diagnosis is being given with increased frequency, which is consistent with the increasing incidence of the disease [15]. In an attempt to further improve the management of patients with TMA, various measures are progressively being developed in a growing number of countries. These include educational programs for generalists, emergency department physicians and all other specialists possibly involved in the management of TMA that increase their understanding of the recognition and management of the disease. Importantly, there should also be educational programs for patients about the typical features suggestive of a relapse.

From the research point of view, TMA represent a fruitful model to better understand the interrelations between microbes, other environmental influences, the immune system and the endothelium within a still uncharted specific genetic background. In this regard, two recent works reported that human leukocyte antigens (HLA) DRB1*11 and DQB1*03 were both susceptibility alleles for acquired TTP and confirmed the protective role of DRB1*04 [16,17]. Future large-scale studies should lead to the identification of additional risk factors associated with acquired idiopathic TTP and in other forms of

TTP, such as those that afflict HIV-infected patients and small ethnic groups in whom the disease occurs at a high frequency. Obviously, our ability to increase our knowledge and experience in the field of TMA was challenged in the past by the low incidence of these diseases and their heterogeneity. However, over the past few years, several national groups have set up large registries that include hundreds of patients with various forms of TMA and these reports have shed light on the epidemiology, clinical presentation, prognosis, and long-term outcome of the diseases [8,18–25]. Those works also provide evidence that collaborations at the national and international level remain key to the continued advancement of the knowledge and treatment of rare diseases. Collaborative works have progressively led to the proposal of consensual treatment modalities and the definitions of treatment responses based on large series of patients. Though arbitrary and based only on clinical experience, these definitions are progressively and advantageously shared by different groups and may foster a common language that can allow for fruitful meta-analyses in the future. There is no doubt that the understanding of TMA requires a tight collaboration between multiples disciplines, including hematology, nephrology, internal medicine, immunology and intensive care medicine. The inter-disciplinary features of these diseases definitively make TMA fascinating diseases that enrich those who dedicate their time to the study of them.

In this special issue of *Presse Médicale* devoted to TMA, acknowledged experts in the field provide a comprehensive series of reviews about the majority of the TMA syndromes and give their views on how the novel pathophysiological mechanisms identified in the laboratory for over 10 years have helped progressively shape new pathophysiological hypotheses and therapeutical attitudes.

Disclosure of interest: Paul Coppo is member of the Clinical Advisory Boards of Baxter and Alexion.

References

[1] Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998;339(22):1585-94.

[2] Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B *et al.* von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 1998;339(22):1578-84.

[3] Moake JL, Rudy CK, Troll JH, Weinstein MJ, Colannino NM, Azocar J *et al.* Unusually large plasma factor VIII:von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med 1982;307(23):1432-5.

[4] Moake JL, Turner NA, Stathopoulos NA, Nolasco LH, Hellums JD. Involvement of large plasma von Willebrand factor (vWF) multimers and unusually large vWF forms derived from endothelial cells in shear stress-induced platelet aggregation. J Clin Invest 1986;78(6):1456-61.

[5] Scheiflinger F, Knobl P, Trattner B, Plaimauer B, Mohr G, Dockal M *et al.* Non-neutralizing IgM and IgG antibodies to von Willebrand factor-cleaving protease (ADAMTS-13) in a patient with thrombotic thrombocytopenic purpura. Blood 2003; 102(9):3241-3.

[6] Caramazza D, Quintini G, Abbene I, Coco LL, Malato A, Di Trapani R *et al.* Rituximab for managing relapsing or refractory patients with idiopathic thrombotic thrombocytopenic purpura–haemolytic uraemic syndrome. Blood Transfus 2010;8(3):203-10.

[7] Froissart A, Buffet M, Veyradier A *et al.* First-line rituximab efficacy and safety in patients with acquired idiopathic thrombotic thrombocytopenic purpura experiencing a suboptimal response to therapeutical plasma exchange: results of a prospective multicenter phase 2 study. Crit Care Med 2012;40(1):104-11.

[8] Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H *et al.* A phase II study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood 2011;118(7):1746-53.

[9] Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. N Engl J Med 2009;360(5):544-6.

[10] Legendre CM, Babu S, Furman RS, Sheerin NS, Cohen DJ, Gaber AO, Eitner F, Delmas Y, Loirat C, Greenbaum LA, Zimmerhackl LB. Safety and Efficacy of Eculizumab in aHUS Patients Resistant to Plasma Therapy: Interim Analysis from a Phase II Trial. Congress of the American Society of Nephrology, 2010.

[11] Muus P, Legendre CM, Douglas K, Hourmant M, Delmas Y, Herthelius BM, Trivelli A, Loirat C, Goodship TH, Licht C. Safety and Efficacy of Eculizumab in aHUS Patients on Chronic Plasma Therapy: Interim Analysis of a Phase II Trial. Congress of the American Society of Nephrology, 2010.

[12] Lapeyraque AL, Malina M, Fremeaux-Bacchi V, Boppel T, Kirschfink M, Oualha M *et al.* Eculizumab in severe Shiga-toxin-associated HUS. N Engl J Med 2011;364(26): 2561-3.

[13] Jilma-Stohlawetz P, Gorczyca ME, Jilma B, Siller-Matula J, Gilbert JC, Knobl P. Inhibition of von Willebrand factor by ARC1779 in patients with acute thrombotic thrombocytopenic purpura. Thromb Haemost 2011;105(3):545-52.

[14] Chen J, Reheman A, Gushiken FC, Nolasco L, Fu X, Moake JL *et al.* N-acetylcysteine reduces the size and activity of von Willebrand factor in human plasma and mice. J Clin Invest 2011;121(2):593-603.

[15] George JN, Gilcher RO, Smith JW, Chandler L, Duvall D, Ellis C. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: diagnosis and management. J Clin Apher 1998;13(3):120-5.

[16] Coppo P, Busson M, Veyradier A, Wynckel A, Poullin P, Azoulay E *et al.* HLA-DRB1*11: a strong risk factor for acquired severe ADAMTS13 deficiency-related idiopathic thrombotic thrombocytopenic purpura in Caucasians. J Thromb Haemost 2010;8(4): 856-9.

[17] Scully M, Brown J, Patel R, McDonald V, Brown CJ, Machin S. Human leukocyte antigen association in idiopathic thrombotic thrombocytopenic purpura: evidence for an immunogenetic link. J Thromb Haemost 2010;8(2):257-62.

[18] Raife T, Atkinson B, Montgomery R, Vesely S, Friedman K. Severe deficiency of VWF-cleaving protease (ADAMTS13) activity defines a distinct population of thrombotic microangiopathy patients. Transfusion 2004;44(2):146-50.

[19] Bentley MJ, Lehman CM, Blaylock RC, Wilson AR, Rodgers GM. The utility of patient characteristics in predicting severe ADAMTS13 deficiency and response to plasma exchange. Transfusion 2010; 50(8):1654-64.

[20] Cataland SR, Yang SB, Witkoff L, Kraut EH, Lin S, George JN *et al.* Demographic and ADAMTS13 biomarker data as predictors of early recurrences of idiopathic thrombotic thrombocytopenic purpura. Eur J Haematol 2009;83(6):559-64.

[21] Hovinga JA, Vesely SK, Terrell DR, Lammle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. Blood 2010;115(8):1500-11 ([quiz 1662]).

[22] Lotta LA, Mariani M, Consonni D, Mancini I, Palla R, Maino A *et al.* Different clinical severity of first episodes and recurrences of thrombotic thrombocytopenic purpura. Br J Haematol 2010;151(5):488-94.

[23] Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, Bettinaglio P *et al.* Genetics of HUS: the impact of MCP, CFH and IF mutations on clinical presentation, response to treatment and outcome. Blood 2006;108(4):1267-79.

[24] Coppo P, Schwarzinger M, Buffet M, Wynckel A, Clabault K, Presne C *et al.* Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. PLoS One 2010;5(4):e10208.

[25] Fujimura Y, Matsumoto M. Registry of 919 patients with thrombotic microangiopathies across Japan: database of Nara Medical University during 1998–2008. Intern Med 2010;49(1):7-15.