Haematologica
Journal of Hematology
volume 85 – number 4 – April 2000

Haematologica 2000; 85:337-339

Editorial and Views

Thrombotic thrombocytopenic purpura: now is the time for clinical trials

In 1924, Moschcowitz published the report of a young woman who died from an illness characterized by hemolytic anemia, fever, bleeding, and neurologic and renal abnormalities.[1] Over the next three decades, many other cases of thrombotic thrombocytopenic purpura (TTP) were reported and the clinical picture and pathologic changes of TTP were revealed. However, the etiology remained unknown and no therapy was available. As a consequence, until the early 1960s, TTP was a fulminant and fatal disease, with fewer than 3% of the patients surviving.[2]

In the next two decades, substantial advances were made. The primary role of platelet clumping was identified[3] and the presence in plasma of a platelet agglutinating factor was hypothesized.[4] In the meanwhile, a series of reports revealed the extraordinary efficacy of plasma exchange,[5] and TTP became a curable disease with a response rate of about 80%. Moreover, it became apparent that plasma infusion alone was sometimes effective,[6] thus suggesting that plasma exchange was able to modify the natural history of TTP by both removing *some harmful, circulating substance* and replacing *a deficient factor*.

Over the last two decades a lot of experimental work has been done to define the etiopathology of TTP further, but no clear conclusion has been reached. Despite many ancillary drugs having been tested in addition to plasma exchange, no large prospective randomized clinical trial have been conducted, and, as a result, therapeutic recommendations are based mainly on anecdotal reports and results in limited number of patients. In addition, it became evident that TTP was a frequent complication of bone marrow transplantation and that plasma exchange was much less effective in this condition.[7] Therefore, twenty years after the introduction of plasma exchange, we are still waiting to know what we have to do for the large number of patients failing to respond to plasma manipulation.

The history of TTP therapy, from some points of view fascinating but from others disappointing, is reviewed in this issue of Haematologica by authors who have a long experience in the clinical management of this illness and have performed some of the few large clinical trials so far available.[8] From this review it is clear that no further improvement will be possible without prospective and randomized clinical trials. Moreover, in the past few months great advances in the field of TTP etiopathogenesis have been achieved, and, at long last, it is now possible to design a clinical trial on the basis of physiopathologic considerations. In fact, in 1998 Furlan *et al*.[9] and Tsai *et al*.[10] came to the same conclusion: non-familial TTP derives from the presence of inhibitory antibodies against von Willebrand factor (vWF)-cleaving protease. Deficiency of this enzyme's activity leads to the accumulation of unusually large multimers of vWF, which in turn are responsible for clumping of circulating platelets. This evidence explains why plasma exchange may be so effective (it removes antibodies against vWF-cleaving protease and replaces fresh protease) and urges us to test the hypothesis that immunosuppressive therapy could further ameliorate the prognosis of TTP-patients. In clear contrast, antibodies against vWF were not observed in bone marrow transplantation-associated TTP.[11] This observation explains the lower efficacy of plasma exchange in this clinical setting and urges us to search for new treatments in this particular form of TTP.

The challenge to improve the results of plasma manipulation in TTP has been accepted recently by two different Italian co-operative groups and two prospective clinical trials are now starting to randomize patients. The first trial (for details, see the website *http://www.ptt-italia.net*) will enroll adult patients with non-familial, non-bone marrow transplantation-associated TTP, and will investigate the role of prednisone therapy (high dose versus standard dose) as adjunctive therapy to plasma exchange. The second trial (for information, write to: *ctmonza@libero.it*) will enroll pediatric and adult patients with TTP following bone marrow transplantation, and will test the efficacy of defibrotide, an antithrombotic drug that obtained good results in veno-occlusive disease following stem cell transplantation[12] and in small series of patients with thrombotic microangiopathy.[13] The efficacy of defibrotide will also be tested in the former clinical trial in those patients who do not respond to first line treatment.

Obviously, we do not know whether these two clinical trials will identify new and more effective strategies for TTP therapy, but we do know for certain that without randomized clinical trials no progress in this field will occur. Therefore, we hope that no single case will escape enrollment and, as a consequence, we will soon be able to treat our TTP patients better.

Prof. Carlo Balduini

Medicina Interna e Oncologia Medica,
Università di Pavia, IRCCS Policlinico S. Matteo, Pavia, Italy.
E-mail: c.balduini@smatteo.pv.it

References

1. Moschcowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: A hitherto undescribed disease. Proc NY Pathol Soc 1924; 24:21-4.
2. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the

literature. Medicine 1966; 45:139-53.
3. Harker LA, Slichter SJ. Platelet and fibrinogen consumption in man. N Engl J Med 1972; 287:999-1005.
4. Lian EC-Y, Arkness DR, Byrnes JJ, Wallach H, Munez R. The presence of platelet aggregating factor in the plasma of patients with thrombotic thrombocytopenic purpura and its inhibition by normal plasma. Blood 1979; 53:333-8.
5. Bukowski RM. Thrombotic thrombocytopenic purpura: a review. Progress Hemostas Thromb 1982; 6: 287-337.
6. Byrnes JJ, Khurana M. Treatment of thrombotic thrombocytopenic purpura with plasma. N Engl J Med 1977; 297: 1386-9.
7. Schriber JR, Herzig GP. Transplantation-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Haematol 1997; 34:126-33.
8. Rock G, Porta C, Bobbio-Pallavicini E. Thrombotic thrombocytopenic purpura treatment in year 2000. Haematologica 2000; 85:410-9.
9. Furlan M, Robles R, Galbusera M, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 1998; 339:1578-84.
10. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998; 339:1585-94.
11. van der Plas RM, Schiphorst ME, Uizinga EG, et al. Von Willebrand factor proteolysis is deficient in classic, but not in bone marrow transplantation-associated, thrombotic thrombocytopenic purpura. Blood 1999; 93:3798-802.
12. Richardson PG, Elias AD, Krishnan A, et al. Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. Blood 1998; 92:737-44.
13. Bonomini V, Frascà GM, Raimondi C, Liviano D'Arcangelo G, Vangelista A. Effect of a new antithrombotic agent (defibrotide) in acute renal failure due to thrombotic microangiopathy. Nephron 1985; 40: 195-200.

HFE, iron homeostasis and genetic hemochromatosis

In the last few years there have been major advances in our understanding of the molecular control of cellular iron metabolism and of molecular genetics of disorders characterized by abnormal iron absorption.

A first fundamental step has been the recognition that the synthesis of transferrin receptor (TfR) and ferritin is regulated by cytoplasmic mRNA-binding proteins, now identified as the iron regulatory proteins (IRPs).[1] IRP1 and IRP2 control the expression of genes involved in iron metabolism whose transcripts contain RNA-stem-loop structures known as iron-responsive elements (IREs). Based on this knowledge, clinical investigators have recently clarified the molecular pathogenesis of the hereditary hyperferritinemia/cataract syndrome (HHCS).[2] This is a new genetic disorder inherited as an autosomal dominant trait and characterized by elevated serum ferritin not related to iron overload and congenital nuclear cataract. Several point mutations in the IRE of ferritin light-chain mRNA have been found in the families so far described.[3,4] These mutations have been shown to prevent IRP binding variably, thus leading to excessive L-ferritin synthesis. HHCS stands as a noteworthy example of a human genetic disorder that arises from RNA mutations within a protein binding site, and in which the energetics of the binding interaction determine the severity of the disease.[5] This exemplifies a new paradigm in which polymorphisms or mutations in mRNA cis-acting elements may be responsible for phenotypic variability in normal and disease states.[6]

Another major step has been the cloning of HFE, the gene of HLA-related genetic hemochromatosis.[7] HFE is an atypical HLA-class I-like gene, mapping approximately 4 megabases telomeric to HLA-A. Since the first report it was considered as a strong candidate gene for hemochromatosis, as most patients were found to be homozygous for a missense mutation changing cysteine at position 282 to tyrosine (C282Y) while other patients were found to carry a second mutation that changes histidine at position 63 to aspartic acid (H63D).[8] It is now well established that most patients with HLA-related genetic hemochromatosis are homozygous for the C282Y mutation while others are compound heterozygotes for C282Y and H63D. Homozygosity for C282Y is found in more than 90% of North Europeans clinically diagnosed with idiopathic hemochromatosis. However, recent studies have shown a lower frequency (64%) for C282Y homozygosity in severely iron-loaded Italian patients.[9] The fact that significant iron loading can occur in individuals with no evidence of HFE mutations or abnormalities in erythropoiesis suggests that genes other than HFE are involved in iron loading.[10] Indeed, juvenile genetic hemochromatosis,[11] the so-called African iron overload,[12,13] and other conditions[14] are examples of genetic syndromes of iron overload due to genes other than HFE. In addition, although HFE-related genetic hemochromatosis is genetically homogeneous, its phenotypic expression is variable, depending on both environmental and genetic factors.[15]

Clearly, iron homeostasis is regulated by several genes that we are just starting to know. The first one, HFE, is far from being fully characterized. Several studies clearly indicate that HFE is involved in the regulation of iron homeostasis[16] and that its mutations are very likely responsible for the human disease.[17,18] However, both the role of HFE in the normal iron metabolism and the mechanisms by which C282Y and H63D disrupt the normal functioning of HFE have yet to be clearly defined. In this issue of Haematologica, a Finnish and an Italian group report on the expression of normal and mutant HFE in different tissues.[19,20] Their works represent steps forward to a deeper insight into the molecular pathogenesis of genetic hemochromatosis.

Mario Cazzola, M.D.,
University of Pavia Medical School, Division of Hematology,
IRCCS Policlinico S. Matteo, 27100 Pavia, Italy.
E-mail: m.cazzola@iol.it