TT30 to block APC-mediated hemolysis. They also demonstrated by flow cytometry that TT30 remained bound to rabbit erythrocytes for more than 24 hours. This observation has important clinical implication as binding of TT30 to covalently bound C3 fragments on erythrocytes could be recognized as a foreign complex (see figure), thereby generating an antibody response that would lead to immune-mediated red cell destruction.

The pharmacodynamic and pharmacokinetic properties of TT30 were studied in cynomolgus monkeys. Bioavailability was demonstrated for both intravenous and subcutaneously injected TT30 with a 3-fold longer duration of complete APC inhibition when injected subcutaneously (24 hours) compared with intravenously (8 hours). Moderate inhibition (60%) of the CPC of relatively short duration (4 hours) was observed for intravenously infused TT30. Immunohistochemical staining of cryosections from healthy and diseased (asthmatically inflamed) lungs demonstrated localization of TT30 to sites of complement activation, supporting the hypothesis that TT30 would be active in controlling APC activation in solid organs.

These studies of Fridkis-Hareli and colleagues have demonstrated the development of a selective inhibitor of the APC with potential for clinical use. But in what pathologic conditions might TT30 be beneficial? An obvious candidate is paroxysmal nocturnal hemoglobinuria (PNH), a disease in which hemolysis is characterized by atypical hemolytic uremic syndrome (a disease that also responds to eculizumab) would be a potential target for TT30 as aberrant regulation of the APC because of inherited mutations of components of the APC underlies the pathobiology of this disease. Conversely, chronic cold agglutinin disease would not be expected to respond to TT30 as activation of the APC by IgM antibody accounts for the complement-mediated hemolysis that characterizes this disease.

Based on the rigorous preclinical studies of Fridkis-Hareli et al, TT30 warrants further development. Determining whether the efficacy of TT30 will be limited by antibody formation against the recombinant protein itself or against neoepitopes created by binding of TT30 to covalently bound C3 degradation product will require further investigation. But to paraphrase Mark Twain, a complaint should always be preceded by a complement.

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REFERENCES


Comment on Pengo et al, page 4714

Home free? Not after 3!

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In this issue of Blood, Pengo and colleagues report a prospective study in which they found that patients who tested strongly positive for all 3 standard antiphospholipid (aPL) assays ("triple positives") had a significant likelihood of experiencing a first thromboembolic event and developing the aPL syndrome (APS).

Unfortunately, patients cannot be diagnosed for APS until after they have already had at least 1 clinical event. Positive laboratory tests alone are not sufficient; the consensus-based definition of the syndrome requires the presence of a clinical manifestation such as a thromboembolic event or defined pregnancy complications for the diagnosis
to be made.² The patient may already have suffered an incapacitating or even fatal event such as stroke, massive pulmonary embolism, or multiorgan failure before the diagnosis is identified. Therefore, finding ways to identify patients who are at increased risk before that first event would be a very valuable contribution because it would open the door to developing preventive treatments.

The finding of positive aPL tests in otherwise asymptomatic patients is not a rare occurrence. Typical situations in which this occurs include preoperative coagulation screening where a prolonged activated partial thromboplastin time is attributed to a lupus anticoagulant, testing for sexually transmitted disease that reveals biologic false-positive syphilis serologies, and diagnostic screens for potential autoimmune condition. However, these laboratory abnormalities are generally dismissed as false positives because they are rarely associated with clinical events. Prophylactic anticoagulation is generally not warranted in these settings because the hemorrhagic risks far outweigh any benefits and many physicians have offered these patients empiric treatment with aspirin; however, this has not been proven effective in at least 1 prospective clinical trial.³ While the current article by Pengo et al was not designed to test the efficacy of the drug, this study also did not find any reduction in thromboembolic events for the patients who were taking aspirin.¹

The uncertainties about the clinical significance of positive aPL tests is attributable to the very nature of the assays themselves. As opposed to virtually all of the other clinical laboratory tests, the aPL assays were not designed to measure a disease-specific analyte or to report on a disease mechanism. Rather, they were derived through careful incremental and often fortuitous empiric observations that were made by astute clinicians over decades. Consider how confusing and irrational the aPL tests must be to the student who is learning about them for the first time! First, there is the lupus anticoagulant, a test that detects neither systemic lupus erythematosus nor a bleeding tendency. Then there are the anticardiolipin antibody IgG and IgM assays, which were developed from efforts to quantify the biologic false-positive syphilis test and are not intended to measure antibodies against cardiolipin at all, but are meant to detect antibodies that recognize β₂-glycoprotein I (B2GPI) and other proteins that are bound to cardiolipin in that assay. Finally, there are the anti-B2GPI IgG and IgM assays that do measure antibodies that are specific for this protein, but whose role in the APS disease process is not yet understood.

It is therefore especially remarkable that Pengo and colleagues were able to show a predictive use for the combination of these nonmechanistic assays.¹ In a well-designed, prospective observational study, they found that patients who tested positive for all 3 of the cardinal aPL tests went on to have a significantly increased risk of developing a thromboembolic event, with an estimated rate of ~5% annually and a cumulative incidence of 37% over the course of the study (see figure). Interestingly, they also identified 2 clinical factors that correlated with increased risk: male sex and a prior risk factor for deep vein thrombosis.

Why should triple positivity be associated with an increased risk for thromboembolism? The simplest and most plausible explanation may be the following: Each of the assays, by itself, has a significant false-positive rate, therefore, triple positivity filters out a group of patients with the lowest likelihood of false positivity and the highest likelihood of having thrombogenic aPL antibodies. Along these lines, my collaborators, Wahezi et al, recently reported that children with autoimmune disorders who were triple positive for aPL tests were also more likely to display resistance to annexin A5 anticoagulant activity than those having a single abnormal aPL test (Wahezi D, manuscript accepted).

Perhaps the most important benefits of this paper by Pengo et al is its contribution to the design of effective primary prevention trials. By identifying these significant predictive risk factors, Pengo et al have identified a subject group that will have a sufficiently high event rate that would allow investigators to test measures that might prevent a first, and potentially devastating, thromboembolic event.¹ Ideally, if there were a sufficient number of subjects, the candidate treatments for a multiarmed trial might include antithrombotic drugs, hydroxychloroquine, and statin agents. Hydroxychloroquine, a synthetic antimalarial drug with immunosuppressive properties, is a particularly attractive candidate because it has an established risk profile, having been used for several decades to treat systemic lupus erythematosus and the drug appears to be associated with reduction of thromboembolic events. More recently, our own laboratory has demonstrated in vitro that the drug interferes with the formation of aPL antibody-B2GPI immune complexes on phospholipid bilayers, with aPL antibody binding to cells, and can also restore annexin A5 crystallization on endothelial and placental trophoblast cell membranes.⁶ It is encouraging that only 2 of the 18 patients in this cohort who were treated with hydroxychloroquine had a first thromboembolic event; however, it must be emphasized that the potential use of this drug will have to be tested in a prospective clinical trial.

The development of precise assays that measure key steps in the aPL disease processes can only come after scientists have elucidated the immunologic and molecular bases for this enigmatic autoimmune thrombophilic disorder. Nevertheless, even before all the definitive answers are known, investigators like Pengo et al will continue to use the current clinical tests to
find successful ways to hit home runs for patients, to prevent and treat this disorder.

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REFERENCES


Comment on Sun et al, page 4723

Complacency is not an option

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Hematopoietic stem cell transplantation (HSCT) survivors do not have an increased risk for anxiety and depression.

Despite the title of a report in this issue of Blood by Sun et al, “Adverse psychological outcomes in long-term survivors of HSCT: A report from the Bone Marrow Transplant Survivor Study (BMtSS),” adverse psychological outcomes are not a significant long-term issue for the majority of transplant survivors. While the impact of an HSCT on the psychological health of a patient and his or her family is not trivial, this finding supports previous research suggesting that the procedure itself does not place long-term survivors at risk for clinical levels of anxiety and depression. This is great news!

Despite this finding, it is important to realize that not all survivors are free of adverse psychological outcomes, and the large sample size from the BMtSS allowed Sun and colleagues to thoroughly examine predictors of psychological distress. Their results suggest that 2 prevailing factors place survivors at risk for psychological distress: perceiving their health status as limited (fair/poor) or receiving prednisone therapy (an agent with a known impact on mood). The degree to which these 2 variables suggest an increased illness burden associated with HSCT or its common effects such as chronic GVHD is less clear; chronic GVHD was not associated with anxiety or depression in this study.

One crucial finding from this study is that survivors who are economically disadvantaged (household annual income ≤ 60,000/year) are at risk for psychological distress. This finding deserves serious consideration because HSCT has long been recognized as an economically burdensome procedure. However, the impact of the financial consequences of the procedure, loss of income, or impact on employability has not been well studied despite reports that HSCT survivors are more likely to report difficulty in holding a job as a result of a health problem such as chronic GVHD. This begs for an operational understanding of how the psychological and social health dimensions overlap, a standard that is recommended in an Institute of Medicine report, “Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs,” which cites specific areas of focus such as financial planning and resources and managing disruptions in work.

While anxiety and depression are common criteria of psychological distress, Sun et al reported somatic distress as an adverse psychological outcome in this study. Somatic distress as assessed by the Brief Symptom Inventory–18 is intended to identify individuals with physical symptoms that represent a mental health disorder. The reader should use caution when interpreting this finding because of the prevalence of late physical effects in this population, well elucidated by other analyses that have been disseminated from the BMtSS sample. When somatic distress can be predicted by a series of clinical factors that suggest a high level of illness burden (eg, active chronic GVHD, severe/life threatening chronic health conditions, and total body irradiation-based regimens), the overlap between the physical aspects of mood disturbances and the common treatment side effects needs to be seriously considered.

While Sun et al concluded that depression and anxiety are not long-term psychological issues in this population, the challenge is to avoid a state of complacency. Routine screening at key intervals throughout the transplant trajectory is critical in identifying individuals experiencing or at risk for adverse psychosocial or quality-of-life effects after HSCT. This study was well designed with a large sample size and a control group of unaffected siblings. Although there are other questions to explore with HSCT survivors, providers need to incorporate the knowledge related to the risks for adverse psychosocial outcomes in this population, as well as cancer patients at large, into standard care for long-term survivors.

In theory, this seems acceptable. In practice, barriers still exist. When an oncology patient presents with complex medical needs, providers are less likely to address their psychosocial health needs, regardless of overwhelming evidence that patients and families can suffer a tremendous emotional burden during complex treatments. While distress screening in HSCT patients has been found to be feasible and accurate, a need still exists to continue to evaluate simple methods of screening such as single item measures like the distress thermometer or an electronic data collection system such as the Patient Reported Outcomes Measurement Information System. If routine screening can start early in the transplant trajectory, an important dialogue can be initiated with HSCT patients about their important psychosocial needs along with self-care approaches related to the management of their whole health (physical, emotional, and social) that will support quality care for many years to come.

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