patients in these 2 groups (scenarios 1 and 2) will subsequently experience thrombosis? How can we identify them so as to prevent these thrombotic events? There are still no evidence-based answers for these questions. The general approach for such patients is to eliminate the secondary risk factors for thrombosis, such as obesity and smoking, and recommend antithrombotic prophylaxis in high-risk situations, such as surgery.7 The benefits of low-dose aspirin for primary prevention of thrombosis are still being debated for patients with APS.8

The Euro-Phospholipid Project9 is the biggest prospective study of APS patients, involving 1000 patients with definite APS (as in scenario 3), and has provided important data in terms of the morbidity and mortality of this syndrome. Ninety-three patients (9.3%) died during 10 years of follow-up; the major causes of mortality were thrombosis (36.5% of all deaths), infections (26.9%), and bleeding (10.7%). Survival rates after 5 and 10 years were found to be 94.7% and 90.7%, respectively.

In the present study, Gebhart et al prospectively investigated 151 LA-positive patients for a median of 8 years.1 At the beginning of the study, 39 patients had no clinical findings attributed to an autoimmune disease (as in scenario 1), 112 patients were diagnosed with APS, and 29 patients had concomitant systemic lupus erythematosus (as in scenario 3). Thirty patients (20%) experienced thromboembolic events during follow-up; 14 of them were arterial thrombosis. During the study period, 20 patients (13%) died: 10 of thrombosis, 5 of bleeding, and 5 of other causes. The cumulative relative survival rate after 10 years was 79.7%, which is very low compared with both the matched reference normal population and APS cohorts of the Euro-Phospholipid Project. The authors showed that new onset of thrombosis was the strongest predictor of poor prognosis, associated with a sixfold increase in mortality. A poor survival rate was not associated with the presence of aCLs and anti-β2GPI antibodies, prior history of thrombosis or pregnancy complications, or prior diagnosis of an autoimmune rheumatic disease in their cohort.1 Furthermore, a new thrombotic event developed under anticoagulant or antplatelet therapy in ~75% of the patients. Interestingly, patients receiving anticoagulant and/or antplatelet therapy showed higher incidences of thrombotic events (23 of 97, 24%) than patients with no therapy (7 of 54, 13%).1 The Euro-Phospholipid Project also showed similar findings.9 There are several possible explanations for why APS patients who were not receiving antithrombotic therapy had lower thrombosis rates. First, patients who were prescribed antithrombotic therapy may have had additional risk factors for thrombosis and may therefore represent a different high-risk group. Second, the results could indicate that current antithrombotic regimens are not effective or sufficient for preventing thrombosis in APS patients. In both Gebhart’s study and the Euro-Phospholipid Project, some patients experienced thrombosis under therapeutic international normalized ratio [INR] values (INR 2-3). Finally, pathologies other than coagulation activation may also contribute to the development of vascular occlusions in some APS patients, including thrombotic microangiopathy, complement activation, and others.

In conclusion, Gebhart et al have clearly shown that the young female patient with LA described above is at increased risk for thrombosis. Our ability to identify higher-risk patients may be improved by better definition of risk factors for thrombosis other than LA and by improved understanding of the unique aspects of the pathophysiology of thrombosis in APS patients.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

© 2015 by The American Society of Hematology

Comment on Buchanan et al, page 3484

The first specific antiplatelet antidote

David Erlinge  Lund University

In this issue of Blood, Buchanan and coauthors present the development of a specific antidote for ticagrelor.1 In fact, this is the first specific antidote against any antiplatelet agent.

Ticagrelor is a widely used reversible adenosine 5'-diphosphate (ADP) P2Y12 antagonist for treatment of patients with acute coronary syndrome (ACS). In the Platelet Inhibition and Patient Outcomes trial, ticagrelor reduced the combined end point of death from vascular causes, myocardial infarction, or stroke for up to 12 months, and even reduced total mortality.2 However, patients also experienced increased bleeding events not associated with coronary-artery bypass grafting (CABG). In the recently published Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 trial, patients with a myocardial infarction 1 to 3 years prior to
enrollment were randomized to 2 different doses of ticagrelor vs placebo.\textsuperscript{3} Even though the study reached its primary end point and demonstrated a significant reduction in ischemic events, this reduction was matched by a similar number of bleeding complications. Furthermore, a patient on ticagrelor cannot undergo urgent CABG or other surgical procedures without increased bleeding risk unless treatment with ticagrelor is interrupted for 3 to 5 days, which increases the risks and causes discomfort for the patient as well as a prolonged hospital stay and higher health care costs.

The development of new antithrombotic medications may have reached its end due to an inevitable increase in bleeding complications when new agents are added: the addition of new antithrombotic drugs on top of already established guideline-directed therapies now often results in a neutral balance between ischemic end points and bleeding complications.\textsuperscript{4,5} Bleeding is associated with increased long-term mortality.\textsuperscript{6} The explanation for this is complex, with contributing factors including increased anemia, blood transfusions, inflammation, surgery, and complications due to prolonged hospital care. For bleeding caused by antiplatelet agents, transfusion of platelets may be of some benefit, but specific treatment is not available.

The antidote against ticagrelor developed by Buchanan et al is a human antibody antigen-binding fragment (Fab) with a high affinity (20 pM) for both ticagrelor and its active metabolite without binding to ADP or other purines. The design of the Fab was improved by crystallographic determination of the Fab-ticagrelor complex. The markedly higher affinity of the antidote (pM) compared to that of ticagrelor for the P2Y\textsubscript{12} receptor (nM) results in elimination of both circulating and P2Y\textsubscript{12}-receptor–bound ticagrelor. In the study, the antidote reversed the antiplatelet effect of ticagrelor in human platelets in vitro, and rapidly restored ADP-induced aggregation in vivo in mice. Furthermore, the antidote normalized ticagrelor-dependent bleeding in a mouse model of acute surgery. The neutralizing effect had a rapid onset within 30 minutes (see figure).

A specific antidote for ticagrelor will be of great value in 2 clinical situations. First, when a patient suffers a life-threatening bleeding complication, the rapid neutralization of circulating ticagrelor may limit the extent of the bleeding, stabilizing the patient and limiting the long-term risk after a bleeding event. Second, a patient acutely treated with ticagrelor for an ACS who needs urgent CABG could undergo surgery within an hour instead of waiting several days. Similarly, a patient on maintenance therapy may undergo noncardiac emergency surgery with limited bleeding risk.

This is the first development of a specific antidote for an antiplatelet agent, fulfilling a long-sought need. For decades, we have used aspirin, clopidogrel, prasugrel, dipyridamol, abciximab, and cilostazol, where the only option for reversal was waiting for systemic elimination of the agent or platelet regeneration, which takes 5 to 10 days. Together with similar developments for newer orally administered anticoagulants such as the antidote idarucizumab for dabigatran,\textsuperscript{7,8} this represents a new era for antithrombotic drug development. It is possible that regulatory demands will increase for a simultaneous development of antidotes before approving antithrombotic drugs. In fact, a phase III study
with available antidote may tip the net balance between anti-ischemic effect and the long-term effects of bleeding complications in a favorable way. It could also be a clinical advantage for newer antiplatelet agents compared to older antiplatelet medications that lack antidotes.

The development of a highly specific, rapid, and potent antidote for ticagrelor is an important achievement with great potential to improve patient safety. The findings in human platelets in vitro and in mice models in vivo are promising. However, clinical studies are needed to confirm the effects in humans.

Conflict-of-interest disclosure: D.E. has received speaker's honoraria from AstraZeneca, Eli Lilly, and Boehringer Ingelheim.

REFERENCES

© 2015 by The American Society of Hematology

Comment on Schneidawind et al, page 3491

A party of three: iNKT cells in GVHD prevention

Annkristin Heine and Peter Brossart  UNIVERSITY HOSPITAL BONN

In this issue of Blood, Schneidawind et al1 demonstrate that the adoptive transfer of CD4+ invariant natural killer T (iNKT) cells and tumor necrosis factor (TNF)-α into the murine model of allogeneic hematopoietic cell transplantation (HCT).

GVHD is one of the most serious complications after allogeneic HCT.2,3 Although advanced treatment options have been approved and new insight into cellular interactions and immune dysregulation has been gained, GVHD still develops in ~40% to 60% of patients.2 T cells are essential for causing GVHD. These alloreactive donor T cells secrete large amounts of proinflammatory T helper (Th)1-biased cytokines such as interferon-γ (IFN-γ), which results in further T-cell activation and expansion. In contrast, a Th2-directed immune polarization can favor GVHD prevention (see figure).2 Various attempts have been made to dampen GVHD, such as the use of Tregs that successfully reduce early expansion of alloreactive donor T cells.3 However, Tregs are rare in peripheral blood, and ex vivo expansion is complex and time-consuming.

NKT cells are a small subset of lymphocytes that bridge innate immune responses to adaptive immunity. They express several cell surface proteins characteristic for T and NK cells. In general, NKT cells are reactive to lipid antigens presented by CD1d major histocompatibility complex class I-like molecules.4 These CD1d-restricted NKT cells can be subclassified into at least 2 groups: one using a semi-invariant T-cell receptor (TCR) (iNKT or type I) and one expressing somewhat more diverse TCRs (type II NKT). Activation of iNKT cells stimulates the rapid release of distinct immunoregulatory cytokines that elicit both Th1 (IFN-γ) and Th2 (eg, interleukin [IL]-4, IL-10, and IL-13) responses. Of note, CD4+ iNKT cells seem to favor the release of Th2-biased cytokines.

The proportion of immunoregulatory iNKT cells in human blood is highly variable and ranges from <0.1% to >2% of the entire T-cell pool. Remarkably, this proportion is thought to be genetically regulated.5 Some studies propose a correlation between low numbers of iNKT cells and the occurrence of autoimmune diseases, whereas transfer of NKT cells suppresses different autoimmune and alloimmune reactions in both animal models and humans.6 These observations have paved the way for clinical translation into the field of allogeneic transplantation and GVHD. For instance, higher amounts of CD4+ iNKT cells in the stem cell graft have been associated with a significantly lower risk of acute GVHD,7 and low peripheral blood iNKT/T-cell ratios after transplant have been identified as an independent risk factor for developing acute GVHD.8 Lastly, adoptive transfer of both donor and host iNKT cells has been described to suppress GVHD in mice.9,10 This effect mediated by iNKT-cell-secreted IL-4 drives Th2 polarization of conventional donor-derived T cells. Moreover, highly purified NKT-cell infusions protected from GVHD development in mice by limiting T cell–mediated secretion of proinflammatory cytokines such as IFN-γ and tumor necrosis factor α.10

Compared to Tregs, markedly lower numbers of CD4+ iNKT cells can prevent GVHD through inducing a Th2-biased immune response. In a previous study,9 Schneidawind and colleagues revealed the underlying mechanism of this effect by showing that transfer of donor CD4+ iNKT cells provokes a robust expansion of donor CD4+ CD25+ FoxP3+ Tregs. Of note, a ratio of <1:20 of CD4+ iNKT to conventional T cells was sufficient, whereas a ratio of ~1:1 was needed when purified, expanded Tregs were transferred together with conventional T cells. Staining for Helios revealed that it was not inducible Tregs but naturally occurring Tregs contained within...
The first specific antiplatelet antidote

David Erlinge