should be especially encouraging for patients worldwide.

Further advances in myeloma should be expected as second-generation proteasome inhibitors (eg, carfilzomib, NPI-052, MLN9074, CEP-18770) and immunomodulatory drugs (pomalidomide) with varying delivery routes and toxicity profiles are now in early clinical testing along with a large series of drugs targeting novel pathways in this disease.[15] A critical next step building on RVD will be reducing toxicity (one model might be use of weekly bortezomib)[16] and prolonging and maintaining remission through consolidation and maintenance therapy.[17,18] Such advances will require an ongoing team effort, with industry, academia, foundations, and government working together. In this era in which increasing oversight, regulation, and negative media attention threaten to suffocate the interaction of the pharmaceutical industry, academic researchers, and hematologist-oncologists[19] it is refreshing to point to the example of RVD where the significant benefits to patients that result from such positive interactions are apparent. In this light and with respect to the future of myeloma trials and to the prerequisite for close industry–physician interaction, I will quote President Andrew Jackson who, in a different context, famously opined, "Our Union: it must be preserved."

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REFERENCES

1. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood.* 2010;116(5):679-686.
2. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2003;349(26):2495-2502.
3. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood.* 2008;112(8):3115-3121.
4. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol.* 2005;23(15):3412-3420.
5. Stewart AK, Richardson PG, San-Miguel JF. How I treat multiple myeloma in younger patients. *Blood.* 2009;114(27):5436-5443.
6. Jakubowiak AJ, Reece DE, Hofmeister CC, et al. Lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone in newly diagnosed multiple myeloma: updated results of phase I/II MMRC trial. *Blood (ASH Annual Meeting Abstracts).* 2009;114(22):Abstract 132.
7. Kumar S, Flinn IW, Hari PN, et al. Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: encouraging results from the multicenter, randomized, phase 2 EVOLUTION study. *Blood (ASH Annual Meeting Abstracts).* 2009;114(22):Abstract 127.
8. Hoering A, Crowley J, Shaughnessy JD Jr, et al. Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in total therapy protocols. *Blood.* 2009;114(7):1299-1305.
9. Barlogie B, Anaissie E, Haessler J, et al. Complete remission sustained 3 years from treatment initiation is a powerful surrogate for extended survival in multiple myeloma. *Cancer.* 2008;113(2):355-359.
10. Harousseau JL, Avet-Loiseau H, Attal M, et al. Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: long-term analysis of the IFM 99-02 and 99-04 Trials. *J Clin Oncol.* 2009;27(34):5720-5726.
11. Jakubowiak AJ, Kendall T, Al-Zoubi A, et al. Phase II trial of combination therapy with bortezomib, pegylated liposomal doxorubicin, and dexamethasone in patients with newly diagnosed myeloma. *J Clin Oncol.* 2009;27(30):5015-5022.
12. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia.* 2009;23(7):1337-1341.
13. Kim YK, Sohn SK, Lee JH, et al. Clinical efficacy of a bortezomib, cyclophosphamide, thalidomide, and dexamethasone (Vel-CTD) regimen in patients with relapsed or refractory multiple myeloma: a phase II study. *Ann Hematol.* 2010;89(5):475-482.
14. Wang M, Giralt S, Delasalle K, Handy B, Alexanian R. Bortezomib in combination with thalidomide-dexamethasone for previously untreated multiple myeloma. *Hematology.* 2007;12(3):235-239.
15. Stewart AK. Novel therapies for relapsed myeloma. *Hematology Am Soc Hematol Educ Program.* 2009;578-586.
16. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood.* 2010;115(16):3416-3417.
17. Palumbo A, Gay F, Falco P, et al. Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. *J Clin Oncol.* 2010;28(5):800-807.
18. Nair B, van Rhee F, Shaughnessy JD Jr, et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with bortezomib, lenalidomide and dexamethasone (VRD) maintenance. *Blood.* 2010;115(21):4168-4173.
19. Fonseca R, Richardson P, Giralt S, et al. Conflicts of interest, authorship, and disclosures in industry-related scientific publications. *Mayo Clin Proc.* 2010;85(2):197-199; author reply 201-204.

● ● ● CLINICAL TRIALS

Comment on Skolnick et al, page 693

Rethinking warfarin reversal

David Garcia UNIVERSITY OF NEW MEXICO

Warfarin and other vitamin K antagonists are very effective for the treatment and prevention of both arterial and venous thromboembolism. Recombinant factor VIIa may not be as effective as previously thought for the urgent reversal of warfarin.

Even under optimal circumstances a small proportion of patients treated with warfarin will develop serious complications such as intracranial or gastrointestinal hemorrhage. In such situations, the clinician needs to reverse the effect of warfarin as quickly as possible. Administering phytonadione (vitamin K) is a critical element of any warfarin reversal strategy; an intravenous dose of 5 to 10 mg of vitamin K will correct the international normalized ratio (INR; a measure of the anticoagulant effect of warfarin) within 24 hours in most patients.[1] However, with life- or limb-threatening hemorrhage the coagulant potential of the blood must be restored more quickly. Fresh frozen plasma (FFP) has been used for warfarin reversal for decades and is still recommended in consensus guidelines.[2,3] FFP's drawbacks include the inability of quick administration, a significant intravascular volume challenge, and the possibility of rare complications such as transfusion-associated lung injury or blood-borne infection. Recombinant activated factor VII (rVIIa) is a compound approved for the treatment of hemophilia patients with a specific inhibitor. Authors of several anecdotal reports and small case series have suggested that rVIIa may be an effective treatment for warfarin-associated bleeding.

In this issue of *Blood*, Skolnick and colleagues present a series of experiments designed to evaluate the in vivo and ex vivo effects of rVIIa on healthy subjects treated to a therapeutic INR with warfarin.[4] The study found that a punch-biopsy–induced bleeding model did reflect the anticoagulant effect of warfarin: both bleeding duration and bleeding

volume were increased with warfarin treatment. rVIIa did, at least partially, correct ex vivo coagulation measurements such as the prothrombin time and the activated partial thromboplastin time. The effect of rVIIa was also examined on whole-blood assays that include platelets. When 80 mcg/kg rVIIa was given to 24 warfarin-treated subjects with a mean INR of 2.8, both thrombin generation and thromboelastography improved significantly compared with the same measurements in 24 warfarin-treated subjects who received placebo. Despite corrections in these ex vivo measurements, rVIIa failed to reduce warfarin-induced increases in both the bleeding time and total blood loss in the punch-biopsy model. There are 2 possible interpretations of this last finding: either the model did not fully reflect the complex biology of in vivo clot formation (and thus this model does not accurately portray the efficacy of rVIIa in patients with warfarin-associated bleeding), or rVIIa, despite its favorable effect on laboratory measurements, is not an effective antidote for warfarin. Interpreted in the light of a recent review that highlighted the lack of high-quality evidence supporting the efficacy of rVIIa for warfarin reversal,[5] I suggest the current paper should lead clinicians to consider other warfarin reversal strategies (which may include FFP or prothrombin complex concentrates) before giving rVIIa to a warfarin-treated patient who has life-threatening bleeding.

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REFERENCES

1. Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J Thromb Haemost.* 2006; 4(9):1853-1863.

2. Baglin TP, Keeling DM, Watson HG. Guidelines on oral anticoagulation (warfarin): third edition–2005 update. *Br J Haematol.* 2006;132(3):277-285.

3. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(suppl 6):160S-198S.

4. Skolnick BE, Mathews DR, Khutoryansky NM, Pusateri AE, Carr ME. Exploratory study on the reversal of warfarin with rFVIIa in healthy subjects. *Blood.* 2010; 116(5):693-701.

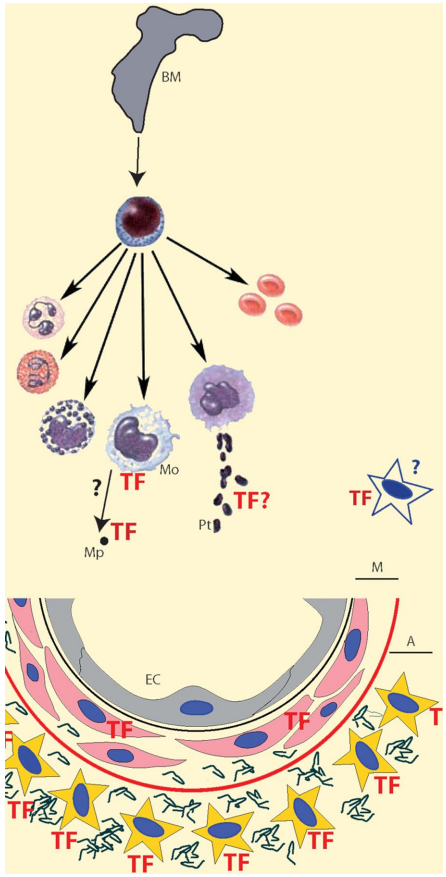
5. Rosovsky RP, Crowther MA. What is the evidence for the off-label use of recombinant factor VIIa (rFVIIa) in the acute reversal of warfarin? ASH evidence-based review 2008. *Hematology Am Soc Hematol Educ Program.* 2008: 36-38.

Comment on Pawlinski et al, page 806

O tissue factor, where art thou?

John H. McVey THROMBOSIS RESEARCH INSTITUTE

In this issue of *Blood*, Pawlinski and colleagues identify myeloid cells and an unidentified nonhematopoietic cell(s) as the source of TF responsible for intravascular coagulation in a mouse model of endotoxemia, excluding a role for EC, VSMC, and platelet cell TF expression.[1]



TF, the initiator of coagulation, is normally not expressed by cells within the vasculature; rather, it is found in the medial (M) and adventitial (A) layers around blood vessels. Endotoxemia induces monocyte (Mo) TF expression that contributes significantly (~ 60%) to the procoagulant response. In mice, platelet (Pt) TF expression is not relevant in this model; however, MP-associated TF does contribute. Endothelial cells and vascular smooth muscle cells do not contribute but an unidentified nonhemopoetic cell type(s) contributes significantly (~ 40%) to the procoagulant response.

The blood coagulation system is normally initiated in response to injury to preserve the integrity of the vascular system. The ability to stem the loss of body fluids from the site of injury is a basic defense mechanism that is essential for the survival of any multicellular organism. The critical need to rapidly form a stable, localized clot in response to injury must be balanced with the need to maintain blood flow within the vessel. The initiation of coagulation occurs when blood is exposed to cells expressing tissue factor (TF). The anatomical distribution of cells constitutively expressing TF has led to the concept that TF forms a hemostatic envelope surrounding blood vessels, organs, and the organism itself. TF is present in medial and adventitial cells including vascular smooth muscle cells (VSMCs), fibroblasts, and pericytes of the blood vessel and serves to limit blood loss after vascular injury. In contrast, cells within the vasculature including endothelial cells (ECs) do not normally express TF, thus maintaining blood flow by presenting an anticoagulant surface. More recently, the identification of "blood borne" TF either on circulating microparticles (MPs) or as a soluble protein, and the possibility that platelets may express TF, has challenged this concept. However, there are contradictory reports about the synthesis and presentation of TF on circulating blood cells and the presence or absence of functionally active TF circulating in blood (see figure).

In endotoxemia, lipopolysaccharide (LPS) induces expression of TF on monocytes and it was believed that this was the major source of TF that contributes to disseminated intravascular coagulation. However, several cell types that come into contact with blood have been shown to synthesize TF in response to a variety of different agonists including LPS. The relative contribution of TF from various cell types to the activation of coagulation in endotoxemia is unknown. Furthermore, although the response of both monocytes and ECs in vitro has been well documented and shown to be very similar, evidence for EC expression of TF in vivo is scant.

In the present study Pawlinski et al investigate the relative contributions of various cell