Emerging Anticoagulant Drugs

Jeffrey I. Weitz

Nowhere is there more clinical trial activity than in the field of anticoagulant therapy. Numerous parenteral and oral anticoagulants are currently undergoing phase II and III evaluation, and many more drugs are in the pipeline. Natural anticoagulants isolated from hematophagous organisms and advances in structure-based drug design have helped to identify new anticoagulant targets and novel mechanisms of action. How can we keep up with this rapidly moving field? A new series, entitled “Emerging Anticoagulant Drugs”, will address this need. With invited articles appearing periodically over the next 12 months, international experts will review the progress in the anticoagulant arena. Each paper will focus on a different drug target.

The first article in this series concentrates on factor IXa. As the enzyme component of intrinsic tenase, the complex of factor IXa bound to factor VIIIa on an anionic phospholipid surface, factor IXa plays a critical role in the amplification of coagulation. The factor VIIa/tissue factor complex initiates coagulation by activating factor X and triggers the generation of small amounts of thrombin, which then activates platelets and factors VIII and V. With further factor X activation by the factor VIIa/tissue factor complex blocked by tissue factor pathway inhibitor, intrinsic tenase amplifies factor Xa generation to produce a burst of thrombin.

The review by Howard and colleagues suggests that factor IXa, critically positioned upstream to factor X, is an attractive target for new anticoagulant drugs. Factor IXa inhibitors attenuate the amplification of coagulation, but can this be done safely in vivo? Lessons from nature suggest that it can. Hemophiliacs deficient in factor IX do not suffer spontaneous hemorrhage unless their factor IX levels are <1%. Levels >5% are associated with a mild phenotype. Therefore, the redundancy of factor IX may serve as a safety valve when factor IXa is inhibited.

Not only does factor IXa represent an obvious target, but novel drugs have been developed to inhibit it. These range from humanized factor IX–directed monoclonal antibodies to factor IXa–binding RNA aptamers or small molecules. Will these drugs make it to the clinic? Which one will be first? How will the benefit-to-risk profile of factor IXa inhibitors compare with those of drugs that block downstream targets, such as factor Xa or thrombin, or agents that inhibit the initiation of coagulation by targeting the factor VIIa/tissue factor complex? Read on!
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