

VTE treatment in 2016 and future challenges

Dr. Mark Crowther in an interview with Dr. Roman Jaeschke: part 3

Dr. Crowther, we are now at the beginning of 2016. We have many more choices in terms of medications we use; how should we be choosing those drugs? What are your principles in this respect?

I think that in 2015 we have a previously unexplored number of choices. There is a couple of patients in whom it is obvious which you should use: a patient who is very unwell, who is in the hospital, who has a high risk of bleeding and may need surgery, unfractionated heparin administered either subcutaneously, or in many cases preferably intravenously, is the drug of choice because it can be stopped and neutralized, and then once the patient is stabilized you can consider other forms of anticoagulation. For uncomplicated inpatients, many of us would choose to use rivaroxaban or apixaban for treatment. These drugs have short half-lives, few drug-drug interactions, and are less expensive than low-molecular-weight heparin. Low-molecular-weight heparin for the long term remains the drug of choice for patients with cancer-associated thrombosis, and warfarin remains the drug of choice for selected patients, for example, those with severe renal insufficiency or patients with heparin-induced thrombocytopenia, the antiphospholipid antibody syndrome, or perhaps some other very high-risk populations of patients.

However, in general I think in 2015 and moving into 2016, for uncomplicated patients we should be regarding the novel agents—rivaroxaban, apixaban, dabigatran, and edoxaban—as the standard of care for patients with venous thromboembolism, unless they have a strong reason to not receive them. Over the long term, I suspect that warfarin and the other vitamin K antagonists will gradually be reduced in the frequency of their use to the point of disappearance. The primary driving force for this is simplicity of use of the new agents and in addition the fact that no one will dispute that warfarin causes a much higher risk of intracerebral hemorrhage and that the rate of dying from bleeding while receiving vitamin K antagonists far exceeds that for the new agents.

Mark, we were talking about the last 20 years, we were talking about new developments in the last year,

we were talking what we are doing now. I wonder if you could give us your thoughts about challenges which will face thromboembolism and hematology during the next few years. What is your opinion here?

In the future, I think we are going to continue to see evolution in our use of the novel agents and, as additional products become available, increasing competition will drive down the cost of these drugs. They are already quite inexpensive and in many cost-effectiveness analyses have been shown to be less expensive than our traditional low-molecular-weight heparin transition to warfarin. However, I think as physicians become more familiar with their use and more confident in their ability to use these drugs, their use will increase. I think what will happen is we will bring people into the anticoagulant population who are currently excluded because of perception of risk.

The other large area where we are just starting to see some progress now is in specific reversal agents. All blood thinners cause bleeding. Dabigatran now has a specific approved reversal agent in the United States, called idarucizumab, and perhaps by the time you are watching this, it will be approved in Canada and elsewhere. Idarucizumab has been shown in a large study to be a highly effective way of reversing the anticoagulant effect of dabigatran, and we would like to think that it also will ameliorate some of the bleeding complications. It is a very nontoxic, simple to administer intravenous bolus that is given in patients with bleeding or patients requiring urgent surgery, which completely neutralizes the effect of anticoagulants.

Other areas where future investigation will be going on include specific reversal agents for the Xa inhibitors. Andexanet alfa is a product being moved through the development pathway by Portola Pharmaceuticals. Should it become available, it will provide specific reversal activity for the Xa inhibitors as well as the low-molecular-weight heparins and unfractionated heparin, and perhaps fondaparinux. They might still be some time away from approval but I think we will have a very well-received market, simply because there is an identified need for drugs that can reverse the Xa inhibitors.

In the future, there is a whole series of new drugs being developed and the hope is that they will be able to uncouple the bleeding risk of current anticoagulants from their antithrombotic effect. Whether this works or not is unclear but it is interesting that drug companies continue to see value in this market, probably because thromboembolism remains a very important cause of morbidity and mortality in the Western population.

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