Extended Treatment of Venous Thromboembolism

Jeffrey Weitz, MD
Professor
Departments of Medicine and Biochemistry and Biomedical Sciences
McMaster University
Canada Research Chair in Thrombosis
Heart and Stroke Foundation Chair in Cardiovascular Research
Hamilton, Ontario

H&O Are there any recent discoveries regarding the causes of venous thromboembolism?

JW There are some thought-provoking basic science observations investigating the link between inflammation and deep vein thrombosis. This work focuses on the role of neutrophils and other inflammatory cells. There is a possibility that these cells release DNA nets, and that these nets form an anchor for the venous thrombi by binding platelets and activating them. These nets might also activate the coagulation system. If this information could be verified in humans, it might open the door to new therapies that either degrade the DNA nets and thereby remove some of the scaffolding for the clot, or possibly prevent clots from forming in the first place by exerting a concomitant anti-inflammatory effect. This potential mechanism could explain why there is a reduction in venous thrombosis associated with drugs that have anti-inflammatory effects, such as statins and perhaps even aspirin.

H&O What types of patients are likely to require extended treatment for venous thromboembolism?

JW The most common scenarios where extended treatment is needed are in patients with ongoing risk factors and in those with unprovoked venous thromboembolism. A common ongoing risk factor is advanced cancer. Patients with venous thromboembolism in the setting of advanced cancer require extended treatment to prevent recurrent clotting. The other common scenario is the patient with unprovoked or so-called idiopathic venous thromboembolism. These patients develop venous thrombosis in the absence of any obvious risk factors, and it is clearly a chronic disease for them. When anticoagulation is stopped in such patients, the rate of recurrent thrombosis is approximately 10% at 1 year and 30% at 5 years. Therefore, these patients are often given long-term anticoagulant treatment.

H&O What is the current approach to management of venous thromboembolism?

JW Traditionally, treatment begins with a rapidly acting parenteral anticoagulant, usually low-molecular-weight heparin. The patient is transitioned to a vitamin K antagonist, usually warfarin. The parenteral anticoagulant is stopped once the international normalized ratio (INR) reaches a therapeutic level. The warfarin is continued for at least 3 months, at which point it is determined whether extended treatment is required or whether a 3-month course is sufficient.

With the introduction of the new oral anticoagulants and the approval of rivaroxaban (Xarelto, Janssen), a factor Xa inhibitor, for treatment of venous thromboembolism, we now have the option to treat these patients with all-oral therapy. They begin treatment with 15 mg of rivaroxaban twice-daily for 3 weeks, and the dose is then reduced to 20 mg once-daily thereafter. At 3 months, a decision is made as to whether or not rivaroxaban therapy needs to be extended; 3 months would be adequate in those with provoked venous thromboembolism, whereas extended treatment is needed for those whose event was unprovoked.
Could you describe your recent study on apixaban for extended treatment of venous thromboembolism?

JW Apixaban (Eliquis, Bristol-Myers Squibb/Pfizer) is an exciting new oral anticoagulant. It is an oral factor Xa inhibitor licensed for stroke prevention in patients with atrial fibrillation. Apixaban was shown to be more effective than warfarin for this indication and was associated with significantly less bleeding. In addition, at the 5 mg twice daily dose, apixaban has a tolerability profile that is at least as good, if not better, than that of aspirin.

The study, known as AMPLIFY-EXT (Apixaban for the Extended Treatment of Deep-Vein Thrombosis and Pulmonary Embolism), was a randomized, double-blind multicenter...
Another limitation of the AMPLIFY-EXT study is that it followed patients for only 1 year. How patients will respond after 2 or 3 years is unknown. In addition, many of the patients in the study were younger than 70. Although it seems likely that older patients will tolerate the drug as well as younger patients, more research is required. Data are also needed regarding patients at more extreme body weights.

H&O Will the study results affect clinical care?

JW The results have an opportunity to influence clinical care. We know that patients with unprovoked venous thromboembolism have a chronic disease and often receive long-term anticoagulation therapy. This study suggests that tapering off the dose after a period of 6 or 12 months can provide a safe and well-tolerated regimen for long-term secondary prevention.

H&O Are there any other promising areas of research?

JW We need to know whether the same phenomenon can occur with the other new oral anticoagulants, such as rivaroxaban. Is it possible to reduce the intensity of dosing with rivaroxaban and achieve the same efficacy profile while reducing the risk of bleeding? The advantage of rivaroxaban is that it is a once-daily drug. There is some recent evidence suggesting that aspirin is useful for secondary prevention in patients with unprovoked venous thromboembolism, but the risk reduction associated with aspirin is about 35%, which is considerably less than the 80–90% risk reduction achieved with anticoagulants. Studies comparing aspirin with one of the new oral anticoagulants would also be useful. We are still refining the management of patients with venous thromboembolism. The new anticoagulants have the potential to simplify and streamline the initial treatment and the long-term treatment. They will likely make management not only easier but also safer for our patients.

Suggested Readings


