THE HISTORY OF ANTICOAGULANTS

FAST FACTS

- Anticoagulants have been used for more than 70 years to prevent and treat potentially deadly blood clots
- Older treatments, including heparins and vitamin K antagonists, have long been the mainstays of treatment. These agents, although effective if managed properly, have significant drawbacks
- By targeting Factor Xa at a pivotal stage in the blood-clotting process, 'Xarelto' inhibits thrombin generation rather than inhibiting the action of thrombin itself

1930s: The advent of heparin

Heparin (unfractionated) has been available for more than 60 years but requires injection, which makes it inconvenient for use out of the hospital setting. It also requires coagulation monitoring, and is associated with heparin-induced thrombocytopoenia (known as HIT, or reduced platelet count) and osteopoenia (low bone mineral density).[1]

1950s: The first oral anticoagulants

Vitamin K Antagonists (VKAs), such as warfarin and acenocoumarol, were the first oral anticoagulants on the market. They are highly effective, but difficult to manage well. For example, these therapies require frequent monitoring and dose adjustment to limit adverse consequences and they have multiple food and drug interactions. These factors, in addition to an increased risk of bleeding and other adverse effects, may contribute to the frequent underuse of warfarin, especially in elderly patients, and low patient satisfaction.[2,3] In addition, VKAs have a slow onset of action, and, when used for VTE treatment, where the patient is at immediate risk of clots, bridging therapy with injected anticoagulants with a fast onset of action is required.

1980s: Overcoming the drawbacks of unfractionated heparin

The low molecular weight heparins (LMWHs) were developed to overcome some of the drawbacks of unfractionated heparin. One of the mainstays of current treatment, enoxaparin, first emerged in 1987. LMWHs do not require monitoring and have a lower risk of HIT,[4] but they must be administered by injection, and can accumulate in patients with kidney impairment.[1]

2000s: DTIs and indirect Factor Xa inhibitors developed

Fondaparinux, an indirect Factor Xa inhibitor, has been shown to be effective, but is also administered by injection, which is inconvenient when long-term use is required. Direct thrombin inhibitors (DTIs) were first introduced in the 1990s. DTIs inhibit the action of thrombin, the enzyme that promotes clot formation. Ximelagatran, the first oral DTI, was not approved in the U.S. and was withdrawn from the European market in 2006 primarily due to severe liver injuries in some patients. Dabigatran, a new oral DTI, was introduced in the European Union and other countries in 2008.

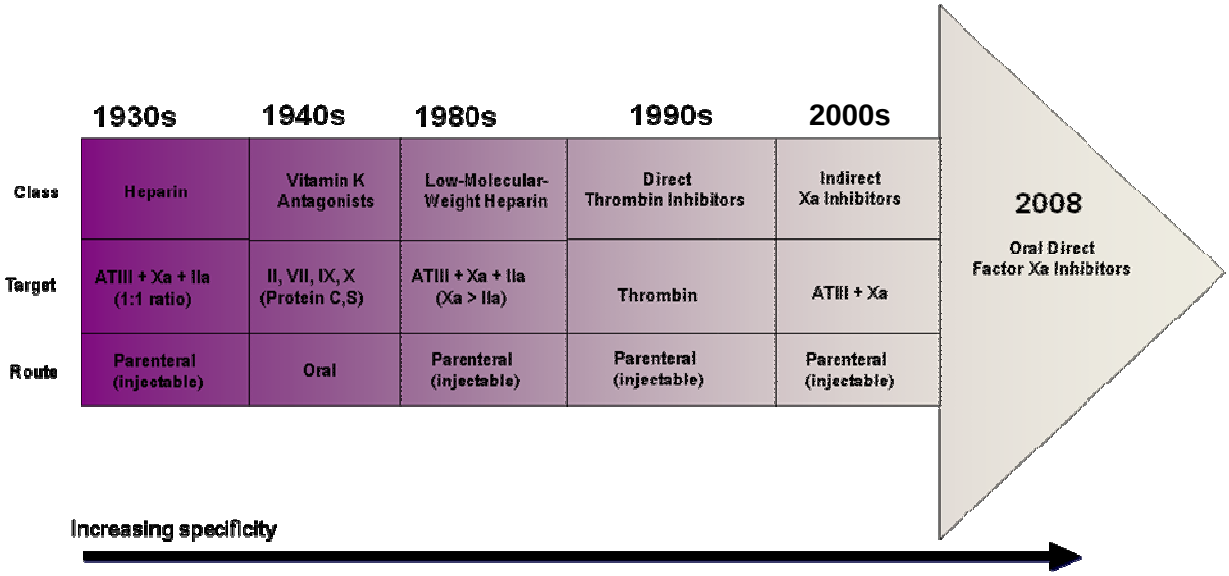
2008: Development of the first oral direct Factor Xa inhibitor

'Xarelto' is a novel, oral direct Factor Xa inhibitor.

Data from four distinct Phase III trials within the RECORD program for VTE prevention following elective (planned) hip or knee replacement surgery showed superior efficacy of 'Xarelto', both in head-to-head comparisons with enoxaparin (RECORD1, 3 and 4) and when comparing extended-duration (5 weeks) 'Xarelto' with short-duration (2 weeks) enoxaparin (RECORD2). In all four trials, 'Xarelto' and enoxaparin had comparable safety profiles, including low rates of major bleeding.

'Xarelto' is also in advanced development in a range of indications for the prevention and/or treatment of potentially deadly blood clots. By targeting Factor Xa at a pivotal stage in the blood-clotting process, 'Xarelto' inhibits thrombin generation rather than inhibiting the action of thrombin itself.

On September 30, 2008, the European Commission granted marketing approval for 'Xarelto' for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective (planned) hip or knee replacement surgery. 'Xarelto' received its first marketing approval in Canada on September 15, 2008, for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip or total knee replacement surgery. 'Xarelto' was submitted in July 2008 for approval to the U.S. Food and Drug Administration (FDA). On approval, Ortho-McNeil, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., will market the drug in the United States. In addition to the FDA submission, filings are under review with regulatory agencies in more than 10 other countries.



To learn more about VTE please visit www.thrombosisadviser.com

To learn more about 'Xarelto' please visit www.xarelto.com

References

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