

New drug development is critical for pharmaceutical companies to maintain a competitive advantage and sustain profits. Novel drug candidates are compounds which emerge from the process of drug discovery. They move through preclinical trials, typically in animals, then on to dose ranging trials in humans (Phase I), and finally to studies on evaluating safety and efficacy in disease state management (Phase II, Phase III). Currently available anticoagulants interrupt thrombus formation, indirectly through interaction with antithrombin, or directly by inhibiting the action of thrombin (Factor IIa). Several agents are available that may offer advances in the prevention and treatment of both venous and arterial thrombosis (1-2).

Rivaroxaban is a oral, direct, specific, competitive Factor Xa inhibitor. It has no direct effect on thrombin and does not require interaction with antithrombin to exert its anticoagulant effect. Rivaroxaban inhibits free and fibrin-bound Factor Xa activity, prothrombinase activity, and Factor Xa generated via the intrinsic or extrinsic coagulation pathway in human plasma (3-4). Rivaroxaban does not directly affect platelet aggregation. There are no dose adjustments with age or extremes in body weight. It does not interact with aspirin, enoxaparin, digoxin, naproxen, ranitidine, or antacids. Rivaroxaban has moved into late Phase III clinical trials (5-6). Most recently the RECORD trials series, 1 through 3, have been reported at the Congress of the International Society for Thrombosis and Hemostasis and the American Society of Hematology Meetings this past year. In the setting of orthopaedic surgery (hip and knee replacement) Rivaroxaban significantly reduced the primary endpoints of deep vein thrombosis (DVT), pulmonary embolism (PE), and all-cause mortality. There were no differences in major bleeding. Future Phase III trials in the setting of atrial fibrillation, acute management of venous thromboembolism, and acute coronary syndromes are now underway.

Apixaban is another investigational oral, direct, reversible Factor Xa inhibitor. It also has a rapid onset and long half life. It represents a follow-up product to Razaxaban, an agent whose development was halted due to a high incidence of bleeding. Apixaban has moved through early dose ranging trials. The APROPOS Study, designed to evaluate the safety and efficacy of Apixaban as thromboprophylaxis in patients following knee replacement. When compared to enoxaparin or warfarin, Apixaban 5, 10, or 20 mg, had a lower composite rate of DVT, PE, and all-cause mortality (7). There was a dose related increase in bleeding. Because of the promising event rate reduction and risk-benefit profile, Apixaban is now being evaluated in trials for acute symptomatic DVT, for VTE prophylaxis in acutely ill medical patients, in patients with non-valvular atrial fibrillation, and in patients with recent acute coronary syndromes.

Dabigatran etexilate is an oral direct thrombin inhibitor. It reversibly binds to free and fibrin-bound thrombin preventing its activity in thrombus formation. Dabigatran etexilate, a pro-drug, is rapidly converted to the active agent, Dabigatran, after oral administration. It has a rapid onset, within 2 hours and a long duration of action, which facilitates once or twice daily dosing. Hepatic enzymes systems are not involved with its metabolism,

nor does Dabigatran induce or inhibit the metabolism of other drugs (8). Dabigatran etexilate has been evaluated in the setting of VTE prophylaxis in total hip replacement surgery. In the RE-NOVATE Trial, at doses of 220mg and 150 mg once daily, Dabigatran etexilate was non-inferior to enoxaparin in reducing the events of DVT, PE, and all-cause mortality (9). There were no differences in bleeding events. Furthermore there were no differences in hepatic related adverse events, which has compromised safety with similar oral direct thrombin inhibitors in the past. In a Phase II dose ranging trial in patients with atrial fibrillation (PETRO), dabigatran etexilate, with or without aspirin, performed comparably in reducing embolic events to warfarin (10). In the setting of total knee replacement surgery, two clinical trials, performed in multiple nations (RE-MODEL) and North America (RE-MOBILIZE), have been reported (11). In RE-MODEL, Dabigatran etexilate was proven as effective as enoxaparin (40 mg) for preventing VTE and all cause mortality following knee replacement surgery in 2,101 patients. Bleeding rates observed in the treatment groups were similar. Clinical trials with dabigatran etexilate continue to enroll patients. Results from safety and efficacy trials in the acute and long-term treatment of VTE, treatment of acute coronary syndrome patients, and stroke prevention in atrial fibrillation are anticipated over the next two years.

Idraparinux is a parenterally administered, long acting inhibitor of factor Xa. It's substantially longer half life compared to fondaparinux allows fixed dose, once weekly subcutaneous administration. In the van Gogh trials, idraparinux was compared to standard therapy (subcutaneous low molecular weight heparin or intravenous unfractionated heparin followed by adjusted dose vitamin k antagonist) for treatment of venous thromboembolism (12-13). In patients with deep vein thrombosis, idraparinux over 3-6 months had similar efficacy to that of standard therapy. However in patients with pulmonary embolism, idraparinux was less effective. During a 6-month treatment extension versus placebo, idraparinux was effective in preventing recurrent VTE, but carried a higher risk of bleeding. Most recently, the AMADEUS trial, evaluating the long term treatment of atrial fibrillation with idraparinux was stopped after an excess of bleeding in elderly and renally impaired patients (13). More trials are warranted to select the appropriate dose of this agent in different disease state settings.

In conclusion, there are a number of new oral anticoagulants that may serve as alternative options to unfractionated heparin, low molecular weight heparin and warfarin. As further studies are completed, clinical trial data on these agents will be submitted to the FDA and reviewed for safety and efficacy performance. They may be available for routine physician prescribing as early as 2009.

#### **References for further reading:**

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