Advances in venous thromboembolism

New synthetic anticoagulants with improved efficacy and safety profiles are currently being developed for prophylaxis and treatment of venous thromboembolism

Drugs for the prophylaxis and treatment of thromboembolism are routinely used in patients at risk of developing postoperative venous thromboembolic complications, in the treatment of acute venous thromboembolism (VTE), in the prophylaxis of recurrent VTE and of arterial thromboembolic events in patients with atrial fibrillation, in artificial heart valve replacement and in the prophylaxis of extracorporeal circulation.

Prevention of VTE is currently initiated with immediate-acting anticoagulants, ie, unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Vitamin K antagonists are used for long-term prophylaxis. UFH is monitored by the activated partial thromboplastin time (aPTT), with the aim of a 2- to 3-fold prolongation, and vitamin K antagonists are monitored with the International Normalised Ratio (INR; values should range from 2–4, depending on the indication). In contrast, LMWHs are not monitored for the prophylaxis and treatment of VTE.

The limitations of conventional anticoagulants are major complications (bleeding) and rare but severe side effects. In addition, vitamin K antagonists interact with other drugs or food intake (vitamin K), and problems can also occur during monitoring with prothrombin time reagents. Due to the severe side effects, only 50% of patients receive oral anticoagulant treatment. The drawbacks and complications of the conventional anticoagulants prompted the development of new anticoagulants.

Melagatran/ximelagatran

The oral direct thrombin inhibitor (ODTI) ximelagatran is a double prodrug of melagatran, transformed to melagatran by the enzymes hydrolase and esterase. The molecular weight of this compound is 478 dalton, with a biological half-life of 4–6 hours and up to 70% excretion in the urine. The anticoagulant effect can be determined by measuring aPTT and ecarin clotting time (ECT).

Postoperative prophylaxis of thromboembolism after elective hip or knee surgery was more effective when melagatran (2mg) was administered at the start of the operation (knife to skin), followed by administration of melagatran (SC 3mg) postoperatively and ximelagatran (oral 24mg/twice daily) twice daily the following day, than when enoxaparin (SC 40mg/daily) was started 12 hours before surgery.1 Ximelagatran (36mg/twice daily) was also more effective than dose-adjusted warfarin.2

Treatment of acute thromboembolism and prophylaxis of recurrent events over 6 months with ximelagatran (36mg/twice daily) without coagulation monitoring was as effective as body weight-adjusted enoxaparin followed by oral warfarin with a target range INR of 2–3. Major and minor bleeding complications occurred less frequently than with conventional therapy.3 Prolonged prophylaxis of recurrent thromboembolism was highly effective over 18 months using ximelagatran (oral 24mg/twice daily), compared with placebo.4,5

The incidence of systemic embolic events per year was reduced (p = 0.018) in patients with nonvalvular atrial fibrillation using ximelagatran (36mg/twice daily), compared with dose-adjusted warfarin with a target INR of 2–3. Bleeding complications occurred less frequently with ximelagatran (p = 0.007).6

In patients with unstable angina and non-Q-wave myocardial infarction (MI), a dose-finding study with ximelagatran (24–60mg/twice daily) administered in combination with aspirin (160mg/daily) revealed an additional benefit of the combination for preventing major cardiovascular events such as MI, severe unstable recurrent angina and mortality during the 6 months of treatment. Major bleeding complications were rare, increasing from 0.9% (aspirin alone) to 1.8% (combination groups).7

Subcutaneous fondaparinux and idraparinux

The synthetic pentasaccharide fondaparinux consists of the antithrombin binding sequence of heparin and LMWH. Fondaparinux is more effective than enoxaparin and equally safe for the prevention of acute deep vein thrombosis (DVT). Fondaparinux (SC

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7.5mg/daily) is as effective and safe as intravenous aPTT-controlled unfractionated heparin (both treatments being followed by administration of vitamin K antagonists to reach an INR of >2) for the initial treatment of acute pulmonary embolism.8

The synthetic hypermethylated pentasaccharide idraparinux displays higher lipophilicity than fondaparinux, and a half-life of 7 days. This drug is given once a week subcutaneously (SC) in the treatment of acute DVT and the prophylaxis of recurrent events over a period of 6 months.

A dose-finding study revealed that 2.5mg is the most effective and best-tolerated dose from a range of 2.5–10mg.9 Large clinical trials are currently being carried out for DVT, pulmonary embolism and prolonged prophylaxis from month 6 to 12 after the initial thrombotic event.

### Oral Factor Xa inhibitors

Several Factor Xa inhibitors are undergoing phase II clinical trials for various indications. A summary is given in the Table 1.

### Determination of anticoagulant effects

Direct thrombin Factor Xa inhibitor effects can be determined by specific methods, ie, coagulation and chromogenic assays. In coagulation assays, values can be expressed as seconds, ratio or concentration of the drug. With chromogenic assays, the concentration of the drug is given as result.

The effects of increasing the concentrations of hirudin, argatroban and melagatran are determined by the ECT. The concentrations of dalteparin (a LMWH), fondaparinux and idraparinux are measured by the Heptest coagulation assay and the chromogenic assay S2222 (Figure 1).10

### Conclusion

These new anticoagulants have a great potential for the prevention and treatment of VTE, due to improved efficacy and safety profiles, compared with conventional anticoagulants such as heparins and vitamin K antagonists.11 The advantage of these compounds is also the fixed dosing and the lack of routine anticoagulant monitoring.

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**Table 1. Antithrombotic therapies in development**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>IV/SC/oral</th>
<th>Action</th>
<th>Indication</th>
<th>Highest status reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>Ximelagatran</td>
<td>Oral</td>
<td>Direct thrombin inhibitor</td>
<td>DVT prevention/ Stroke prevention in atrial fibrillation (SPAF)/post-MI</td>
<td>Registration</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>BIBR-1048MS</td>
<td>Oral</td>
<td>Direct thrombin inhibitor</td>
<td>SPAF</td>
<td>Phase IIa</td>
</tr>
<tr>
<td>Organon Sanofi-Synthelabo</td>
<td>Idraparinux</td>
<td>SC</td>
<td>Factor Xa inhibitor</td>
<td>Thrombosis</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>GlaxoSmithKline Groupe Fournier</td>
<td>SanOrg-34006</td>
<td>SC</td>
<td>Thrombin inhibitor</td>
<td>SPAF/DVT prevention</td>
<td>Phase II</td>
</tr>
<tr>
<td>Daichi</td>
<td>DX-9065a</td>
<td>SC</td>
<td>Factor Xa Inhibitor</td>
<td>Coronary artery disease/Acute coronary syndrome</td>
<td>Phase II</td>
</tr>
<tr>
<td>Bristol-Myers Squib (DuPont)</td>
<td>DPC-423</td>
<td>Oral</td>
<td>Factor Xa inhibitor</td>
<td>N/A</td>
<td>Phase II</td>
</tr>
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<td>Bayer</td>
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<td>Oral</td>
<td>Factor Xa inhibitor</td>
<td>N/A</td>
<td>Phase I</td>
</tr>
<tr>
<td>Tulank/Eli Lilly</td>
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<td>Oral</td>
<td>Factor Xa inhibitor</td>
<td>N/A</td>
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</tr>
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References