Ximelagatran reduced venous thromboembolism more than warfarin after total knee replacement


Clinical impact ratings IM/Ambulatory care ****** Internal medicine ******** Haematology ******☆

Q In patients having total knee replacement, is ximelagatran better than warfarin in preventing venous thromboembolism (VTE)?

METHODS

A randomised controlled trial (Exanta Used to Lessen Thrombosis A [EXULT A]).

Allocation: concealed.*

Blinding: blinded (clinicians, patients, data collectors, outcome assessors, and data analysts).**

Follow up period: 4–6 weeks.

Setting: 116 centres in the US, Canada, Israel, Mexico, and Brazil.

Patients: 2301 patients who were having primary total knee replacement and weighed between 40 and 136 kg. Exclusion criteria included pneumatic leg compression; immobilisation ≥3 days; major surgery, stroke, myocardial infarction, or receipt of study drug <30 days before surgery; increased risk of bleeding ≥90 days before surgery; increased risk of bleeding <90 days before surgery; uncontrolled hypertension; thrombocytopenia; drug or alcohol abuse in the past 6 months; and potential for pregnancy.

Intervention: twice-daily tablets of ximelagatran (Exanta, AstraZeneca), 36 mg (n = 775); 24 mg (n = 762); or once daily warfarin (Coumadin, Bristol-Myers Squibb) (n = 764). Placebos were given for each study drug. Ximelagatran was started ≥12 hours after surgery when haemostasis had been achieved and warfarin was started the evening of the day of surgery and adjusted to achieve an international normalised ratio (INR) of 2.5.

Outcomes: composite primary endpoint of total deep venous thrombosis (DVT), pulmonary embolism (PE), and all cause mortality; and bleeding.

Patient follow up: 2285 patients (99%) (mean age 68 y, 62% women) were included in the safety analysis and 1851 (80.4%) in the efficacy analysis.

*See glossary.
**Information provided by author.

MAIN RESULTS

Fewer patients who received ximelagatran, 36 mg, had an occurrence of the composite primary endpoint than did patients who received warfarin (table). The ximelagatran 24 mg group did not differ from the warfarin group (table). Neither ximelagatran group differed from warfarin for the secondary composite endpoint of proximal DVT, PE, and all cause mortality (p values >0.10). Groups did not differ for bleeding (table).

For correspondence: Dr C W Francis, University of Rochester, Rochester, NY, USA. charles_franics@urmc.rochester.edu

Source of funding: AstraZeneca.

**Commentary

The trial by Francis et al shows the superiority of 36 mg twice daily of ximelagatran over warfarin, both started after surgery, for prevention of VTE after total knee replacement surgery. However, as the greater efficacy came entirely from a decreased incidence of isolated (largely asymptomatic) calf vein thrombosis, the interpretation of these results deserves comment.

In most studies, comparing low molecular weight heparins (LMWHs), which have a rapid onset of action, and oral anticoagulants, which require 2–4 days to render an anticoagulant effect, the latter category of drugs has been less effective. Because the LMWHs and comparator drugs were started at the same time before surgery, I wonder whether the superiority of ximelagatran simply reflects the different onset of action of the 2 drugs. All that oral anticoagulants can do in this setting is prevent thrombus from growing. Indeed, in this trial and in virtually all those assessing LMWHs, the incidence of proximal vein thrombosis and that of PE, when taken together, did not differ between patients receiving oral anticoagulants and those receiving heparin.

Despite this consideration, warfarin is problematic for VTE prophylaxis because of the need for laboratory monitoring and potential drug interactions, and LMWHs are the standard of care for the prevention of VTE after orthopaedic surgery. Although ximelagatran was shown to be more effective than enoxaparin in the EXPRESS study,1 it has not been compared with fondaparinux, a synthetic anti-Xa inhibitor that is more effective than enoxaparin for VTE prophylaxis after orthopaedic surgery. The ultimate comparison of efficacy in the prevention of VTE after orthopaedic surgery may be a head to head comparison between ximelagatran and fondaparinux.

Continued on next page.

**Table: Outcomes after total knee replacement

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>X dose</th>
<th>Event rates</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary endpoint</td>
<td>36 mg</td>
<td>20.3% v 27.6% 26%</td>
<td>(9.9 to 40)</td>
<td>14 (9 to 40)</td>
</tr>
<tr>
<td></td>
<td>24 mg</td>
<td>24% v 27.6% 9.8%</td>
<td>Not significant</td>
<td>(8 to 25)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>36 mg</td>
<td>0.8% v 0.7% 18%</td>
<td>Not significant</td>
<td>(61 to 264)</td>
</tr>
<tr>
<td></td>
<td>24 mg</td>
<td>0.8% v 0.7% 20%</td>
<td>Not significant</td>
<td>(61 to 270)</td>
</tr>
</tbody>
</table>

*Composite primary endpoint = venous thromboembolism, pulmonary embolism, and all cause mortality. Abbreviations defined in glossary: NNT, NNH, and CI calculated from data in article.