Lessons from ximelagatran: issues for future studies evaluating new oral direct thrombin inhibitors for venous thromboembolism prophylaxis in orthopedic surgery

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CRD summary
The authors concluded that the risk-benefit profile of ximelagatran used as thromboprophylaxis in total hip and knee replacement surgery depended on the surgery type, initial timing of administration and probably dose. This was generally a well-conducted review, but given the limited number and heterogeneous nature of the studies, the conclusion should be treated with caution.

Authors' objectives
To identify conditions under which ximelagatran might be superior to current standards for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, DARE, Cochrane Central Register of Controlled Trials (CENTRAL) and Health Technology Assessment Database were searched from 1980 to April 2005 without language restrictions. Conference abstracts from International Society on Thrombosis and Haemostasis (1999 to 2005), American Society of Hematology (1999 to 2005), websites of the ximelagatran manufacturer, Canadian Coordinating Office for Health Technology Assessment and Food and Drug Administration were searched. Search terms were reported. Bibliographies of retrieved articles were handsearched for additional material.

Study selection
Randomised controlled trials (RCTs) that compared thromboprophylaxis using ximelagatran (24mg dose or more twice daily) with unfractionated heparin, low molecular weight heparin or vitamin K antagonists for at least seven days in patients who underwent total hip replacement or total knee replacement were eligible for inclusion in the review.

The main outcome measures were: major venous thromboembolism (occurrence of deep vein thrombosis or pulmonary embolism measured by objective methods) and major bleeding episodes (required surgery, blood transfusion, hospital readmission or haemorrhage in critical sites).

All included studies were industry funded. Included studies compared ximelagatran (24mg or 36mg) with low molecular weight heparin (LMWH, enoxaparin or dalteparin) or warfarin. In four studies, patients in ximelagatran treatment arms initially received subcutaneous melagatran (an active form of ximelagatran). Duration of intervention ranged from six to 12 days. Treatment was started preoperatively or postoperatively.

The authors did not state how many reviewers selected studies for inclusion in the review.

Assessment of study quality
Trial quality assessment was assessed using Jadad criteria (maximum achievable score of 5). Adequacy of allocation concealment was assessed according to criteria of Schultz and Grimes.

Two reviewers independently performed the quality assessment; discrepancies were resolved by consensus.

Data extraction
Two reviewers independently extracted data into standardised electronic forms; discrepancies were resolved by consensus.

Methods of synthesis
A random-effects meta-analysis was used to synthesise odds ratios (ORs) and 95% confidence intervals (CIs,
DerSimonian and Laird model). Heterogeneity was assessed using the $X^2$ test (p value less than 0.1 indicated significant heterogeneity) and the Higgins $I^2$ test (<25% was low heterogeneity, 25-50% was moderate and >50% was high heterogeneity).

Subgroup analysis was performed according to odds ratios with studies grouped by surgery, type of comparator and initial use of melagatran. Sensitivity analysis was performed according to quality scores and allocation concealment, ximelagatran dose, outcomes analysed on intention-to-treat versus as-treatment basis, timing of initiation of comparator and timing of initiation of melagatran/ximelagatran.

Publication bias was investigated using inverted funnel plots.

**Results of the review**

Nine RCTs (n=13,756) were included in the meta-analysis: seven studies were double-blind and had a Jadad score of 5 with adequate concealment; one study scored 3 with unclear concealment; and one study scored 2 with unclear concealment.

All studies (total hip plus knee replacements): There was no significant difference between ximelagatran and comparators in occurrence of major venous thromboembolism. Ximelagatran was associated with a significant increase in major bleeding (OR 1.58, 95% CI 1.04 to 2.39; nine studies, n=6,361). High heterogeneity was found for venous thromboembolism ($I^2$=74.3%). Moderate heterogeneity was found for major bleeding ($I^2$=34.8%).

**Type of surgery:** Among patients who underwent total knee replacement, ximelagatran was associated with significantly fewer major venous thromboembolism events than comparators (OR 0.68, 95% CI 0.53 to 0.89). There was no significant difference in occurrence of major bleeding. No heterogeneity was found.

**Initial timing of administration:** Among total hip replacement patients started on melagatran/ximelagatran before surgery, ximelagatran was associated with significantly fewer major venous thromboembolism events compared with low molecular weight heparin (OR 0.32, 95% CI 0.19 to 0.53) but had a significant increase in major bleeding events (OR 3.33, 95% CI 1.88 to 5.89).

**Dose:** Among patients (all underwent knee replacement) who received ximelagatran 36mg, ximelagatran was associated with significantly fewer total venous thromboembolism events than comparators (OR 0.64, 95% CI 0.55 to 0.75). There was no difference between treatments in major venous thromboembolism or major bleeding events.

Publication bias was not detected.

**Authors' conclusions**

The risk-benefit profile of ximelagatran (and possibly other similar agents) used as thromboprophylaxis in total hip and knee replacement depended on the surgery type, initial timing of administration and probably dose.

It should be noted that the authors stated that ximelagatran was withdrawn by the manufacturers due to severe hepatic toxicity.

**CRD commentary**

This review addressed a clear research question supported by clear inclusion criteria. The authors searched several relevant databases without language restrictions, which reduced the risk of language bias. Unpublished data was sought, which minimised risk of publication bias. Validity was assessed and most studies scored high. Methods were used to minimise reviewer error and bias during data extraction and validity assessment; it was unclear whether similar appropriate methods were used for study selection. Pooling data in the presence of high heterogeneity may not have been appropriate. However, heterogeneity was investigated with subgroup and sensitivity analyses. Generally this was a well-conducted review and the authors' conclusions reflected the results. Given the limited number of studies and even fewer studies within the subgroup and sensitivity analyses, the conclusions should be treated with caution.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies that evaluated new direct thrombin inhibitors should take into account factors found in this review to influence outcomes (such as type of surgery and timing of drug administration).

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