Trials and Tribulations of Noninferiority: The Ximelagatran Experience

The review of noninferiority trial design in the November 8 issue of JACC (1) takes a critical view of the SPORTIF III and V trials, which compared ximelagatran to warfarin in patients with atrial fibrillation. Kaul et al. (1) confuse statistical issues with pharmacological limitations of ximelagatran and problems associated with double-blind versus open-trial design. In many ways, the study traces the arguments in the U.S. Food and Drug Administration statistical review leading to rejection of the ximelagatran marketing application by the agency last year. We take issue with several points:

1. The noninferiority margin reflects an estimate of the proportion of warfarin efficacy that might be lost in exchange for certain therapeutic advantages. There is more focus on the predefined delta than on the results, which were consistent with noninferiority for margins down to 0.13%/year for SPORTIF III, 1.03%/year for SPORTIF V, and 0.44%/year for the prespecified pooled analysis of primary outcomes. Selection of the 2% margin was based on an expected warfarin event rate of 3.1%/year and judgment about the difference that would be clinically meaningful (2). The observed rates on warfarin were lower, as were the upper limits of 95% confidence.

2. The investigators (1) regard the expected warfarin rate as unrealistic, though it was based on previous trials adjusted for risk factors (3). Warfarin efficacy is not homogeneous in absolute terms for secondary prevention. Patients with prior thromboembolism comprised 21% of the cohort of the 6 previous studies of warfarin, including the European Atrial Fibrillation Trial (4); the SPORTIF trials had the same proportion. An inherent weakness of historical assessment of warfarin efficacy is that the only previous double-blind trial included no women (5).

3. Kaul et al. (1) acknowledge that retention of 50% of warfarin efficacy as a prerequisite for noninferiority is arbitrary. To preserve this level of efficacy, the relative delta in the SPORTIF trials would have been 1.471. Kaul et al. (1) divide the assumed warfarin event rate by the absolute margin to arrive at a relative margin of 1.65. Calculated conservatively from meta-analyses of earlier studies, the relative delta would be about 1.4. Although the noninferiority criteria applied to the SPORTIF trials compared absolute differences, relative rate ratios for ximelagatran/warfarin (95% CI) follow:
   - SPORTIF III 0.713 (0.477, 1.065)
   - SPORTIF V 1.390 (0.913, 2.116)
   - Pooled analyses 0.982 (0.737, 1.308)

   The results of SPORTIF III and pooled analyses meet the relative margin criterion of 1.4. As with any reasonable relative margin, however, SPORTIF V was inconclusive.

4. Neglecting SPORTIF III and the pooled results overlooks not only the hard end points, blinded evaluations, and exhaustive measures to minimize bias, but also neglects the generalizability of observations to clinical practice. Although noninferiority can be questioned for SPORTIF V, ximelagatran was undeniably noninferior in both SPORTIF III and in the pooled results according to even the most conservative assessment.

5. Kaul et al. (1) consider noninferior efficacy for stroke prevention undermined by liver toxicity. While potentially deleterious effects must be considered in balancing risks and benefits, this goes beyond the noninferiority assessment for efficacy in the primary analysis.

Over a span of 11,346 patient-years (mean 18.5 months/patient) in the SPORTIF trials, primary events occurred in 93 patients given warfarin and 91 given ximelagatran: rates of 1.65%/year and 1.62%/year, respectively (difference −0.03; 95% CI −0.50 to 0.44%/year, p = 0.94). Even with careful warfarin adjustment, ximelagatran caused less bleeding. The trials were not designed to evaluate the potential for ximelagatran to cause hepatotoxicity, and developing ways to manage that risk requires additional research.

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REFERENCES


