ORIGINAL ARTICLE

Genetic Determinants of Response to Warfarin during Initial Anticoagulation

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ABSTRACT

BACKGROUND

Genetic variants of the enzyme that metabolizes warfarin, cytochrome P-450 2C9 (*CYP2C9*), and of a key pharmacologic target of warfarin, vitamin K epoxide reductase (*VKORC1*), contribute to differences in patients' responses to various warfarin doses, but the role of these variants during initial anticoagulation is not clear.

METHODS

In 297 patients starting warfarin therapy, we assessed *CYP2C9* genotypes (*CYP2C9* *1, *2, and *3), *VKORC1* haplotypes (designated A and non-A), clinical characteristics, response to therapy (as determined by the international normalized ratio [INR]), and bleeding events. The study outcomes were the time to the first INR within the therapeutic range, the time to the first INR of more than 4, the time above the therapeutic INR range, the INR response over time, and the warfarin dose requirement.

RESULTS

As compared with patients with the non-A/non-A haplotype, patients with the A/A haplotype of *VKORC1* had a decreased time to the first INR within the therapeutic range (P=0.02) and to the first INR of more than 4 (P=0.003). In contrast, the *CYP2C9* genotype was not a significant predictor of the time to the first INR within the therapeutic range (P=0.57) but was a significant predictor of the time to the first INR of more than 4 (P=0.03). Both the *CYP2C9* genotype and *VKORC1* haplotype had a significant influence on the required warfarin dose after the first 2 weeks of therapy.

CONCLUSIONS

Initial variability in the INR response to warfarin was more strongly associated with genetic variability in the pharmacologic target of warfarin, VKORC1, than with CYP2C9.

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