Ximelagatran—Promises and Concerns

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Vitamin K (“Koagulation”) antagonists have been the sole oral anticoagulants available for 60 years, ever since Link⁴ identified the components in spoiled sweet clover responsible for bleeding in cattle. Originally developed as a rat poison, vitamin K antagonists such as warfarin are used successfully for the prevention of venous and arterial thromboembolism for a wide range of clinical indications, including atrial fibrillation (AF), venous thromboembolism (VTE), coronary artery disease, some orthopedic procedures, and congenital or acquired thrombophilia. Since both age and obesity increase the risk of atrial fibrillation and VTE, the need for anticoagulants is increasing.

Warfarin treatment is complicated by several inherent problems that have limited its use. These include delayed onset of its antithrombotic action, narrow therapeutic index, unpredictable and variable pharmacological response, and the mandatory regular laboratory monitoring to control its anticoagulant effect and minimize risk of serious bleeding. In addition, numerous drugs, certain dietary supplements, alcohol, and even some foods markedly influence warfarin dose response.⁵ As a consequence, a higher level of patient diligence and reliability is required than with almost any other drug; furthermore, warfarin management is labor intensive for the physician and is not reimbursed. In addition, there is the discomforting realization that whereas the hemorrhagic effects of warfarin are visible and often dramatic (usually dose-related), the benefits are imperceptible to the individual patient.

The overall annual incidence of major hemorrhage due to oral anticoagulants has ranged from 1.2% to 7.0%,⁴ but is lower (0.5%-4.2%) in clinical trials with rigorous management of selected patient populations.⁵ In general practice, vitamin K antagonists remain a leading iatrogenic cause of hospitalization. For instance, in France, among an estimated 500,000 patients treated each year with anticoagulants, 17,000 are hospitalized annually for hemorrhagic events.⁶

Unquestionably, less complicated anticoagulants are needed. Ideally, these agents should be available in both parental and oral formulations, have prompt onset of action, have a predictable dose response not requiring laboratory monitoring, and should not interact with other drugs. The profile of ximelagatran, the oral form of the antithrombin agent melagatran, fulfills these requirements, so trials of its clinical effects have been followed with keen interest for some time.

Thrombin is the enzyme generated by the coagulation cascade and is directly responsible for clotting fibrinogen and aggregating platelets. Inhibitors of thrombin or antithrombins are effective natural anticoagulants. For instance, hirudin (from the medicinal leech Hirudo medicinalis) and its analogues such as hirulog, argatroban, and melagatran are highly specific thrombin inhibitors that have been developed only for short-term clinical use, since they must be administered parenterally. Melagatran is a small dipeptide analogue which, unlike hirudin, binds only to the active site of thrombin and binds reversibly. This property is relevant since melagatran has been associated with less bleeding than is seen with tighter-binding inhibitors.⁸ Like the other direct antithrombins, melagatran inhibits not only free thrombin but also clot-bound thrombin, whereas heparin inhibits only the former. Melagatran also has a more predictable anticoagulant effect than heparin, since it is not protein cofactor–dependent.

Ximelagatran is a prodrug form of melagatran, which enables it to be rapidly absorbed in the small intestine. After absorption, ximelagatran is bioconverted to its active form, melagatran, which has about 20% bioavailability.⁹ After ingestion of ximelagatran, peak blood levels of melagatran are reached in 2 to 3 hours; its antithrombotic activity is immediate, and it is cleared entirely by renal excretion within 12 hours.

At therapeutic doses, melagatran induces prolongation of prothrombin time, partial thromboplastin time, and thrombin time, but since the effect is predictable at a fixed dose, monitoring these parameters is unnecessary. A specific antidote is not available, but when renal function is unimpaired, the rapid clearance of melagatran limits its effect. However, intravenous activated prothrombin complex or activated factor VII preparations could be used to more promptly attenuate the anticoagulant effect of melagatran.¹⁰ No specific food or drug interactions have been reported.

See also pp 681, 690, and 699.
More than a dozen studies in 4 clinical indications (orthopedic surgery, VTE, post myocardial infarction, AF) have been published, in which a combined total of almost 14000 patients were randomly assigned to receive a fixed-dose of ximelagatran compared with patients receiving low-molecular-weight heparin, warfarin, or both. Seven trials were for the primary prevention of VTE in patients undergoing total hip or total knee replacement surgery, and the drugs were administered for about 12 days.\textsuperscript{13,14,16} The efficacy of ximelagatran in preventing postoperative VTE was comparable to standard therapy in 4 studies\textsuperscript{11,12,15,17} and was significantly more effective in 3.\textsuperscript{13,14,16} In 1 study,\textsuperscript{18} in which ximelagatran treatment was initiated with subcutaneous melagatran administered before surgery, severe bleeding was more frequent than with low-molecular-weight heparin, but in the remainder of trials no differences in the incidence of bleeding were found. As of October 2004, ximelagatran had been marketed in 7 countries in Europe for VTE prophylaxis in hospitalized patients undergoing joint replacement surgery,\textsuperscript{19} at a dose of 24 mg twice daily for up to 11 days.\textsuperscript{19} Postmarketing clinical information is not yet available.

The secondary prevention of VTE by ximelagatran was evaluated in a trial in which patients were recruited after they had completed 6 months of standard treatment for acute VTE.\textsuperscript{11} Thereafter, 1233 patients were randomly allocated to receive ximelagatran (24 mg) or placebo twice daily. During 18 months of follow-up, symptomatic recurrent VTE developed in 71 patients (11.6%) in the placebo group, compared with only 12 events (1.9%) receiving ximelagatran. Major nonfatal hemorrhage occurred in 5 patients receiving placebo and 6 receiving ximelagatran. As in other trials, ximelagatran was associated with a 6% incidence of asymptomatic increases in alanine aminotransferase (ALT) levels to more than 3 times the upper limit of normal. This decreased over time whether or not the drug was discontinued.\textsuperscript{20}

Secondary prophylaxis initiated within 14 days after an acute myocardial infarction was evaluated in 1883 patients randomized to receive ximelagatran (24, 36, 48, or 60 mg) or placebo twice daily for 6 months. All patients received 160 mg aspirin daily. Ximelagatran significantly (P<.05) reduced cardiovascular events during the observation period. Major bleeding occurred in 1.8% of patients receiving ximelagatran compared with 0.9% in the placebo group.\textsuperscript{21}

In a major clinical study reported in this issue of JAMA, Fiessinger and colleagues,\textsuperscript{22} on behalf of the THRIVE Investigators, present the findings from a 279-center, multinational study of acute VTE. A total of 2489 patients with deep vein thrombosis were randomized to receive either ximelagatran alone (36 mg twice daily) or low-molecular-weight heparin (enoxaparin) followed by warfarin. One third of the patients in each group had associated pulmonary embolism, but patients with pulmonary embolism causing hemodynamic instability were excluded, as were those with deep vein thrombosis of longer than 2 weeks duration and obesity. Patients and physicians were blinded to the 6 months of treatment, necessitating placebo injections as well as sham regular laboratory testing. The incidence of recurrent VTE was comparable and remarkably low in both groups—2.1% and 2.0% with ximelagatran and enoxaparin/warfarin, respectively. This is about half the rate anticipated with conventional therapy, a finding the authors suggest may have been related to the complexity of the study leading to selection of healthier patients. Since regular surveillance with ultrasonography was performed, plus venography if distal deep vein thrombosis was suspected, it is unlikely that cases were overlooked.

The incidence of major bleeding complications during the 6-month treatment period was also low (ximelagatran, 1.3%; enoxaparin/warfarin, 2.2%), without any apparent differences in the sites at which bleeding occurred. Also noted was a locally reported incidence of 10 (0.8%) serious coronary events in the ximelagatran group compared with 1 (0.08%) in the enoxaparin/warfarin group. Such a finding has not been previously reported. It is noteworthy that this association was not found in the large AF trials, which were of longer duration, and that ximelagatran specifically prevented coronary events when this indication was evaluated.\textsuperscript{21} Ximelagatran was associated with an asymptomatic increase (>3 times the upper limit of normal) of ALT levels in 9.6% of patients, slightly higher than in other studies, but this compared with a 2% incidence in the enoxaparin/warfarin group. The increase occurred at a mean of 2.5 months after initiation of treatment and resulted in the discontinuation of ximelagatran in 76 patients (6%), which was mandated by the protocol if the increase exceeded 5 times the upper limit of normal.

The findings from the study by Fiessinger et al suggest that fixed-dose ximelagatran is as effective as, and is possibly safer than, the more complicated regimen of low-molecular-weight heparin/warfarin for the standard course of treatment of acute VTE (without major pulmonary embolism). At the same time, the authors caution that the mechanism and clinical relevance of the increases in ALT levels require further evaluation.

Atrial fibrillation is a condition with an established long-term risk of potentially devastating thromboembolism and remains notoriously undertreated using oral anticoagulants.\textsuperscript{23} Atrial fibrillation is one of the prime indications for an oral anticoagulant that is more predictable and less demanding of both patients and physicians. After an initial dose-ranging study in nonvalvular AF,\textsuperscript{24} the European open-label SPORTIF III study was conducted in which 3410 patients were randomized to receive fixed-dose ximelagatran (36 mg twice daily) or dose-adjusted warfarin and then followed up for a mean duration of 17.4 months. The primary event rates in this study were similar (1.6% per year for ximelagatran and 2.3% per year for warfarin), and the combined major and minor bleeding rates were slightly lower with ximelagatran (25.8% vs 29.8%).\textsuperscript{25}

The SPORTIF III study has now been followed by a North American trial, reported by Halperin and colleagues\textsuperscript{26} on be-
half of the SPORTIF V investigators in this issue of JAMA. The design was identical to the European study except for the important difference that treatment was double-blind. A total of 3922 patients who had AF and at least 1 additional thromboembolic risk factor (74% had more than 1) were included, making it the largest such study of stroke prevention in AF with ximelagatran reported. During a mean follow-up of 20 months, strokes or systemic emboli occurred with comparable frequency (1.2% per year with warfarin and 1.6% per year with ximelagatran), and overall mortality was the same. Rates of major bleeding were 3.1% per year and 2.4% per year with warfarin and ximelagatran, respectively. Rates of minor bleeding were significantly lower with ximelagatran, and the authors observed a correlation between bleeding and use of low-dose aspirin in both treatment groups. Increases in serum levels of ALT occurred with ximelagatran in 6% of patients (0.8% with warfarin), typically within the first 6 months, and returned to baseline spontaneously or after stopping the drug. One patient developed hepatic necrosis and at autopsy showed a pattern of resolving hepatitis (viral antibody titers not reported), and another with a markedly increased ALT level (>11 times the upper limit of normal) developed a fatal gastrointestinal hemorrhage.

Halperin et al call attention to the relevant fact that the quality of anticoagulant control of warfarin in the study is seldom achieved in practice. The results of this study confirm the findings from the open-label SPORTIF III that the efficacies of ximelagatran and warfarin in preventing arterial emboli in patients with nonvalvular AF are comparable and that major and minor bleeding events were somewhat lower with ximelagatran.

O’Brien and Gage27 have taken the data from these studies of AF and have subjected them to a challenging cost-benefit analysis, which is also published in this issue of JAMA. The authors’ calculations were predicated on the AF studies’ findings that ximelagatran and warfarin have identical rates of stroke but with ximelagatran having a lower (0.74) hemorrhagic risk, a $1280 per year higher cost, and a marginally higher quality of life utility value (0.989 compared with 0.987 for warfarin). Based on these principal assumptions, the results were expressed in terms of quality-adjusted life-years and US dollars. Their analysis led the authors to the sobering but inescapable conclusion, related to established criteria, that ximelagatran was not likely to be cost-effective except in patients with AF and a high bleeding risk, a low utility value, or low quality of life with warfarin.

However, certain of the fundamental differences between these 2 drugs affect some of the assumptions underlying this analysis and may warrant reconsideration of this conclusion. For example, the authors note that calculation for the cost-effectiveness of ximelagatran was “exquisitely sensitive to its effectiveness” in stroke prevention, for which the 2 drugs were rated equal. However, the efficacy of warfarin is directly related to the quality of its anticoagulant control, which was quite exceptional in these studies of selected populations under unusually strict supervision. Comparable efficacy is unlikely to be achieved in general practice.28 While double the stroke rate with warfarin is more typical.28 By contrast, since ximelagatran is given at a fixed dose without any monitoring for anticoagulant control, there is little reason to believe its efficacy in these clinical trials cannot be duplicated in general practice. The authors suggest that the short half-life of ximelagatran makes it especially susceptible to lapses in adherence, but this problem pales in comparison with that of maintaining the narrow therapeutic range of warfarin in the face of its innumerable food, drug, and lifestyle interactions.

Second, the utility value—to which the calculations were also sensitive—assigned to warfarin is surprisingly high, being little different from that assigned to ximelagatran. This value was based on a previous survey of 83 patients with AF but in which 16% of patients “rated the utility of warfarin so low that their quality-adjusted life expectancy would be greater with aspirin.”29 More important, the utility value of 0.987 is difficult to reconcile with the authors’ acknowledgment that warfarin is currently prescribed for only half of the patients with AF who are candidates for anticoagulation. Even if this poor utilization were attributable to some lack of education, the uniquely complicated nature of warfarin management cannot be dismissed as a significant contributing factor. A utility value for warfarin more commensurate with the well-established limits of its use would have significantly increased the relative cost-benefit calculation for ximelagatran.

Third, ximelagatran is a less complicated, more user-friendly anticoagulant, making it a potentially more acceptable and less intimidating alternative to warfarin. These qualities should help overcome much of the current reluctance associated with anticoagulant prophylaxis and encourage its use in the treatment of a substantially higher percentage of patients with AF, or those at risk of VTE, than is currently the case. Since 2.3 million Americans have AF and a stroke risk of at least 0.2% to 2% per year,30,31 a substantially higher number of debilitating and costly strokes could thereby be prevented. Although speculative, providing anticoagulation to this large population could increase the clinical effectiveness of ximelagatran even if its efficacy were equivalent to warfarin.

The principal caveat concerns the increased ALT levels associated with ximelagatran and the concern that some hepatotoxicity may occur with longer-term use. O’Brien and Gage27 estimate 1 death from hepatic failure among 2300 patients treated, based on 3 deaths with liver failure reported in the trials. A causal relationship is difficult to establish and has not been established definitively, but the mechanism responsible for the enzyme changes remains to be established.

While there is no evidence that short-term use (≤11 days), such as for knee and hip replacement surgery, is associated with a risk of hepatotoxicity, patients in these studies were only followed up for 4 to 6 weeks after surgery; delayed hepato-
totoxicity was not assessed.32 However, analysis of data from longer-term exposure suggests that signs of liver injury as reflected by elevations of ALT levels were typically observed after 1 to 2 months in approximately 6% of patients receiving ximelagatran therapy.32 Accordingly, if ximelagatran is prescribed, monitoring of liver function test results is warranted to detect early signs of liver injury and to possibly prevent more severe hepatotoxicity.

With respect to the more troublesome possibility of long-term adverse effects from the drug, it seems unlikely that yet another clinical trial will resolve this question. Diligent postmarketing surveillance is essential to monitor use and to determine the risks associated with this agent, and this may be the best, if not the only, way to deal with this question. It is possible that such data will become available from Europe, but this is unlikely at present since for now only short-term use has been approved. In the United States, the Food and Drug Administration, perhaps feeling the effects of recently having to withdraw drugs from the market, has denied approval of ximelagatran because of concerns about hepatotoxicity.33 However, this precaution concerning the risk of hepatotoxicity from ximelagatran must be balanced against the serious risk of discouraging, if not foreclosing indefinitely, any improvement in oral anticoagulant therapy, which remains an important and growing therapeutic need.

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REFERENCES

1. Link KP. The anticoagulant from spoiled sweet clover. Harvey Lect. 1943;34:162.