Editorials
A promising advance in anticoagulant therapy for patients with atrial fibrillation

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(Ital Heart J 2004; 5 (5): 335-339)

Received March 11, 2004;
accepted March 15, 2004.

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Initiating long-term oral anticoagulation in atrial fibrillation (AF) demands considerable clinical acumen. How much protection against stroke or other thromboembolic events does anticoagulation offer this patient? What is the risk of bleeding or other complications? Within the working lifetime of almost all doctors in clinical practice today, the answers to these questions have largely depended on the properties of a single class of anticoagulant agents: the vitamin K antagonists (VKAs), such as warfarin. Yet even though VKAs have a proven efficacy in this setting, reducing the stroke risk by 68% in randomized controlled trials[1], their use is fraught with well-known difficulties.

The prevailing, evidence-based treatment guidelines in AF[2,3] represent an attempt to negotiate this problematic risk-benefit profile by stratifying patients on the basis of their thromboembolic risk. VKAs are preferred, unless contraindicated, for patients with any high-risk factor (age ≥ 75 years, left ventricular systolic dysfunction, or a history of stroke, transient ischemic attack, systemic embolism, or hypertension) or any combination of moderate-risk factors (age 65-75 years, diabetes mellitus, coronary artery disease in the absence of left ventricular dysfunction)[2]. For lower-risk patients (those aged ≤ 65 years who are free of cardiovascular disease or risk factors), anticoagulation is not recommended. Antiplatelet therapy with aspirin, although less efficacious, is deemed more appropriate[2]. Despite these valuable guidelines, however, warfarin and other VKAs remain widely underprescribed[4,5], and even when they are prescribed, the resulting quality of anticoagulation control is often disappointing[6,7]. Overall, stroke preventive therapy for patients with AF is suboptimal[8]. Against this background, the publication[9] of positive results from a randomized clinical trial with ximelagatran – the first in a new class of agents termed oral direct thrombin inhibitors – may prove to be a seminal event. The results of the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III trial suggest that the risk-benefit profile of ximelagatran in this indication is superior to that of warfarin[10].

Ximelagatran is an oral direct thrombin inhibitor, the active form of which is melagatran[11]. Approximately 20% of an oral ximelagatran dose becomes bioavailable as melagatran, which binds noncovalently and reversibly to both fibrin-bound and freely circulating thrombin. Oral ximelagatran, in its active form, not only inhibits thrombin activity rapidly, competitively, and potently, but also delays and suppresses thrombin generation. In patients with AF, ximelagatran normalizes the circulating levels of a marker for systemic hypercoagulability, platelet P-selectin[12].

SPORTIF III (n = 3407) was a pivotal, phase III, open-label randomized clinical trial in patients with nonvalvular AF[9], conducted at 259 centers in Europe, Asia, and Australasia. The trial was undertaken to determine whether oral ximelagatran therapy, administered at a fixed dose of 36 mg twice daily, without coagulation monitoring, can prevent stroke (ischemic or hemorrhagic) and systemic embolic events as effectively as well-controlled, dose-adjusted warfarin (INR 2.0-3.0)[9].

The SPORTIF III trial design reflects an important aspect of the history of thrombo-

prophylaxis in AF. The current treatment guidelines[2,3] are based on evidence from earlier, placebo-controlled trials demonstrating the efficacy of currently available agents[13-16]. In this context, designing trials of newer anticoagulant agents to show superiority over placebo would be ethically difficult to justify. SPORTIF III was therefore designed to test the efficacy of the study drug, in terms of statistical noninferiority, relative to an active comparator of proven efficacy. As the main aim of the trial was to assess the thromboprophylactic value of oral ximelagatran in AF, the most appropriate active comparator was the prevailing treatment of choice for AF patients with a moderate-to-high thromboembolic risk, i.e., dose-adjusted warfarin (INR 2.0-3.0). Accordingly, the recruitment criteria for all of the randomized clinical trials in the SPORTIF program (SPORTIF II, III, and V) largely resembled those employed in the earlier clinical trials with warfarin[13-16]. To further enhance the reliability of the findings, all endpoint events were adjudicated by an independent central committee, the members of which were blinded to treatment.

Outcome analysis in SPORTIF III showed that the total exposure to treatment in the ximelagatran (n = 1704) and warfarin (n = 1703) groups was 4941 patient-years (mean 17.4 months per patient)[9]. By intention-to-treat analysis, primary endpoint events were observed in 40 patients in the ximelagatran group, compared with 56 patients in the warfarin group. The primary event rate was 1.6%/year with ximelagatran vs 2.3%/year with warfarin – an absolute risk reduction of 0.7% (95% confidence interval-CI -0.1 to 1.4, p = 0.10). Oral ximelagatran therefore met the prespecified criteria for noninferiority relative to warfarin. For the prescriber, this means that oral ximelagatran protects moderate-to-high risk AF patients against thrombosis at least as effectively as the current standard therapy.

Strengthening the reliability of this finding, the control of warfarin-mediated anticoagulation in SPORTIF III[9] was similar to that achieved in the earlier randomized trials with warfarin in AF[13-16]. The mean INR was 2.5 ± 0.7, with warfarin-treated patients spending 66% of follow-up within the INR target range of 2.0-3.0, and 81% of follow-up within the extended target range of 1.8-3.2. The adherence to therapy in the ximelagatran group, as estimated by pill counts, was 94%[9].

Discussion of the risks associated with antithrombotic therapy logically begins with the reported incidence of bleeding. In SPORTIF III, hemorrhagic stroke was observed in 4 ximelagatran-treated patients (0.2%/year) vs 9 warfarin-treated patients (0.4%/year, p = 0.266); the strokes were fatal in 3 and 5 patients respectively[9]. Comparisons between treatment groups revealed no significant differences in mortality or in the rates of disabling or fatal stroke, major bleeding, or study drug discontinuation related to major bleeding. The incidence of major gastrointestinal, subdural, or intraocular bleeding was identical or similar in the two groups; bleeding at other critical extracranial (e.g., pericardial, retroperitoneal, articular, or spinal) sites was reported only in the warfarin group. The combined incidence of major and minor bleeding was lower in the ximelagatran than in the warfarin group (25.8 vs 29.8%/year respectively; relative risk reduction 14%, 95% CI 4 to 22, p = 0.007)[9].

The SPORTIF III treatment groups generally did not differ in the incidence of other adverse events, with the exception of elevations in serum alanine aminotransferase (ALAT). Elevations of ALAT > 3 times the upper limit of normal were detected in 107 patients in the ximelagatran group (6%), as compared with 14 patients (1%, p < 0.0001) in the warfarin group. Among the ximelagatran-treated patients in whom this finding was reported, elevation of ALAT typically began 2-6 months after treatment initiation, but typically returned toward the pretreatment baseline regardless of whether ximelagatran therapy was continued or discontinued (59 vs 48 patients respectively). Moreover, ALAT elevations were typically not associated with specific clinical symptoms. All 4 of the patients in the ximelagatran group who developed jaundice had other potentially icterogenic conditions: gastric carcinoma with hepatic metastases in 1 patient and gallstones in the other 3 patients (2 of whom also had a further risk factor for jaundice – hepatitis B and exposure to flucloxacillin respectively)[9].

The other pivotal phase III trial of oral ximelagatran in AF, SPORTIF V (n = 3922), was conducted at 409 centers in North America. The only respect in which the design of this trial differed from that of SPORTIF III was that treatment administration in SPORTIF V was double-blind[17]. For patients in the ximelagatran group, INR management was mimicked with sham testing and administration of dummy warfarin in varying doses. At the time of writing, the publication of the final, detailed results from SPORTIF V is pending. The preliminary results, however, have been presented in abstract form[18], and broadly appear to confirm those of SPORTIF III. Disabling or fatal stroke, hemorrhagic stroke, and major bleeding occurred at similar rates in the two SPORTIF V treatment groups. The final results of a prespecified pooled analysis of SPORTIF III and V are also pending.

A comprehensive account of the risk-benefit profile of oral ximelagatran should also consider the broader difficulties associated with implementing the treatment guidelines in AF, including the various barriers to anticoagulation prescription and to patient acceptance and adherence[5]. In the pivotal clinical trials[13-16] that furnished the evidence base for the current guidelines on anticoagulation[2,3], the quality of anticoagulation control with warfarin generally did not surpass the 66% attained in SPORTIF III[9]. These findings are consistent with reports that warfarin-treated patients with AF reportedly spend only 40-50% of the time within the target range[6,7]. Even more strikingly, an estimated 50-

85% of eligible AF patients are never prescribed warfarin[4,5]. The barriers to warfarin prescription appear to include a variety of factors related to patients, physicians, and the health care system, although the relative importance of these factors remains to be determined[5].

During the odyssey of long-term oral anticoagulation, the prescriber of warfarin steers a narrow course between the Scylla of thrombosis and the Charbydis of bleeding. Indeed, the clinical literature often refers to the line between these hazards as a "tightrope"[19,20]. A possible basis for this remarkably narrow therapeutic index has been identified in preclinical studies. In a rat model of arterial thrombosis, the dose increment required to increase the antithrombotic effect of warfarin from 25 to 75% was only 2-fold. In contrast, the corresponding dose increment for ximelagatran was 10-fold[21]. In keeping with these findings, the overall balance between efficacy and safety has been judged acceptable in clinical studies with oral ximelagatran in which the total range of doses was at least 3-fold[9,18,22-25]. As VKAs affect coagulation indirectly, via suppression of vitamin K-dependent coagulation factors, their onset of action necessitates several days. An additional, major limitation of currently available oral anticoagulant agents is that dose requirements are unpredictable, largely because the pharmacokinetic profile of the VKAs is highly variable. For example, drug-drug interactions with warfarin are myriad. Dose requirements are also susceptible to pharmacogenetic variations[26], generic substitution[10], intake of food or alcohol and dietary vitamin supplementation.

In this context, raising the standard of anticoagulation in everyday practice challenges us to identify the pharmacological limitations of currently available therapies, and to tackle these limitations at the molecular level. By targeting thrombin directly, oral ximelagatran avoids several limitations associated with the indirect inhibition of coagulation via antagonism of vitamin K. For example, its pharmacodynamic profile suggests that oral ximelagatran is less likely than warfarin to have a narrow therapeutic window. In addition, its onset and offset of antithrombotic action occur on a time scale similar to that seen with the low-molecular-weight heparins[22], and include antiplatelet and profibrinolytic in addition to anticoagulant actions.

In studies with healthy volunteers, oral ximelagatran has exhibited a stable and predictable pharmacokinetic profile, with minimal intra- and interindividual variation during single or repeated dosing[27,28]. Similar findings have been obtained in several populations of patients, including patients with AF[29]. Dosing requirements for ximelagatran appear independent of age[30], gender[29], ethnicity[31], obesity[32], and intake of food or alcohol[33]. Moreover, oral ximelagatran exhibits a low potential for interaction with drugs metabolized by hepatic cytochrome P450 enzymes (CYPs), including CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4[34]. This pharmacokinetic profile suggests that the dose requirements for oral ximelagatran are substantially less likely to vary than those for warfarin.

Overall, the clinical pharmacology of oral ximelagatran, combining the favorable pharmacodynamic and pharmacokinetic properties outlined above, is compatible with long-term, fixed-dose anticoagulant therapy, without coagulation monitoring. The 94% patient adherence to oral ximelagatran in SPORTIF III[9] is consistent with the possibility that, in every clinical practice, patients with AF may find such a therapeutic approach readily acceptable.

What difference is oral ximelagatran likely to make to the prescriber contemplating initiation of long-term anticoagulation for a patient with AF and a moderate-to-high thromboembolic risk? Already, the literature in general medicine as well as in cardiology is contemplating the possibility that ximelagatran will systematically replace warfarin in this indication[10,35]. The evidence from the SPORTIF program published to date[9,12,18,23,24,29] suggests that, compared with warfarin, oral ximelagatran offers patients with AF antithrombotic protection of at least equal efficacy, while reducing the overall risk of bleeding. At the same time, direct thrombin inhibition with ximelagatran introduces the option of rapid-onset, fixed-dose oral anticoagulation, without coagulation monitoring, and greatly reduces the potential for interactions with other medications, alcohol, or food. The clinical significance of the association of ximelagatran with the elevation of ALAT in a small proportion of cases remains under investigation.

Elevation of ALAT was observed in 6% of patients in SPORTIF III, but the typically transient pattern of these elevations suggests that long-term monitoring of ALAT in patients receiving oral ximelagatran therapy is unlikely to be required. In those cases where ALAT elevation was observed, it was typically transient, with the ALAT levels typically returning toward normal regardless of whether treatment was continued or discontinued. SPORTIF III reported no association between ALAT elevations and specific symptoms or clinical or pathological outcomes in ximelagatran-treated patients. Further analysis of the clinical trial data will provide a basis for more detailed recommendations in the future.

Clinicians and patients alike have waited several decades for anticoagulant therapy to address the limitations of warfarin and other VKAs. The prospect of fixed-dose anticoagulation with an oral direct thrombin inhibitor is therefore a therapeutic development of singular promise. Tangible evidence of this promise has emerged recently, with the first regulatory approval of oral ximelagatran. In December 2003, France (acting as the reference member state under the EU Mutual Recognition Procedure) granted oral ximelagatran an *autorisation de mise sur le marché* for the prevention of venous thromboembolism (i.e., deep venous thrombosis, with or without pulmonary embolism) in patients

undergoing elective hip or knee replacement surgery. While a more complete picture may be expected with the publication of the final results from SPORTIF V, the results from SPORTIF III already provide considerable evidence favoring recognition of oral ximelagatran in the setting of AF.

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