The Potential for Changing Prescribing Patterns from Warfarin to Oral Direct Thrombin Inhibitors: Clinical Scenarios

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Ximelagatran, a direct thrombin inhibitor, is currently being considered by the US Food and Drug Administration (FDA) for approval as an anticoagulant to manage thromboembolic disorders and prevent systemic embolism in patients with atrial fibrillation. If ximelagatran is approved, clinicians will have to decide which patients are candidates for this therapy, how to switch patients from warfarin to ximelagatran, and, if necessary, how to switch patients from ximelagatran to warfarin. In addition, clinicians will need to consider their approach to treating patients with new-onset atrial fibrillation as well as conditions that may require an adjustment in dosing. This article highlights some of these issues as well as current data that provide guidance on how to manage them; however, answers to other questions will not be available until after the FDA approves the package insert material and data from the SPORTIF trial become available. Therefore, clinicians should diligently follow the medical literature regarding the latest information on this agent.

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The oral direct thrombin inhibitor ximelagatran[1-3] is currently being considered by the U. S. Food and Drug Administration (FDA) for approval as an anticoagulant in the management of venous thromboembolic disorders and for prophylaxis against systemic embolism, including embolic stroke, in patients with atrial fibrillation (AF). If ximelagatran is approved for use by the FDA, practitioners will require assistance in integrating the drug into their clinical practice. The purpose of this article is to initiate the assistance process.

Assumption 1: Ximelagatran Is Approved by the FDA for Use in Patients with AF

If we assume that such approval is forthcoming, and if we limit our discussion to the use of ximelagatran in AF patients, the following questions will need to be addressed.

- Which patients will be candidates for treatment with ximelagatran?
- Which patients will not be candidates?
- What process(es) will be required to transfer a patient from warfarin to ximelagatran?
- Which patients might possibly require transfer from ximelagatran to warfarin, and how?

Because of ximelagatran's short half-life pharmacokinetic profile,[4-6] to some extent we might model our approach on the last 2 questions, which relate to our experience in shifting between heparin or low-molecular-weight heparin (LMWH) congeners and warfarin.

Table 1
Atrial Fibrillation (AF) Candidates for Ximelagatran

Definite
Patients with nonvalvular AF and current indications for warfarin, eg:
Age ≥65 y
Hypertension
Diabetes mellitus
Heart failure/LV dysfunction
Prior systemic embolus, embolic stroke, TIA
Uncertain
Patients not included in the clinical trials, eg, those:
With rheumatic valvular disease
With prosthetic heart valves
With advanced or unstable renal disease
Not yet anticoagulated who are to undergo elective cardioversion
Contraindicated
Patients who should not receive ximelagatran for anticoagulation:
Pregnant patients
Patients in whom liver function tests cannot be evaluated (because of hepatic disease or, possibly, concomitant use of other drugs)

LV, left ventricular; TIA, transient ischemic attack.

AF Patients Who Will Be Candidates for Ximelagatran

Patients with AF who will be candidates for ximelagatran include those who (1) are at increased risk for thromboembolic events—as have been identified in published guidelines such as those established by the American College of Chest Physicians (ACCP)[7] and a partnership of the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC),[8]—and (2) do not have any of the exclusion criteria that were used in the pivotal AF trials of ximelagatran during its development process: Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Nonvalvular Atrial Fibrillation (SPORTIF) III and V (Table 1).[9-11] The former includes those patients with AF who are now considered for treatment with warfarin, whereas the exclusions used in SPORTIF will somewhat reduce the size of this group. Though the ACCP and ACC/AHA/ESC guidelines vary slightly, they share high-risk markers: hypertension (or a history of hypertension), diabetes mellitus, left ventricular (LV) failure, age ≥65 years, and/or prior stroke or systemic embolism (SEE). To enrich their population for events, the SPORTIF III and V trials modified these identifiers and enrolled patients with persistent or paroxysmal chronic nonvalvular AF plus 1 or more of the following: prior stroke, transient ischemic attack (TIA), or SEE; hypertension; LV dysfunction; age ≥ 75 years; and age ≥ 65 years with diabetes or coronary artery disease. Exclusions in SPORTIF included patients under age 18 years, pregnant patients, patients who were to undergo elective cardioversion, patients with prosthetic heart valves, and patients with chronic valvular heart disease (primarily rheumatic). Exclusions were primarily for ethical reasons. Because ximelagatran's utility has not yet been proven in populations of AF patients who meet the SPORTIF exclusion criteria, it is unlikely that such patients will be approved as candidates for the drug when it is released by the FDA for use in clinical practice.

AF Patients Who Will Not Be Candidates for Ximelagatran

The abovementioned exclusions notwithstanding, because ximelagatran has been proven noninferior to warfarin in a wide spectrum of patients, both with AF and with venous thromboembolic disorders,[10-18]

Table 2
Indications for Switching from Warfarin to Ximelagatran

Noncompliance with prothrombin time testing schedules
Experienced or potential food or drug interactions with warfarin
Nonbleeding complications on warfarin
Patient preference
Physician preference

it would seem highly likely that the same relationship would also hold true in most AF patient groups in which the 2 agents have not yet been tested head to head. Thus, it is likely that ximelagatran will be used off-label in clinical practice in some additional patient groups, such as those with valvular heart disease (excluding those with prosthetic heart valves) and in those who are to undergo elective cardioversion but are otherwise identical to the population described above. However, for ethical reasons related to uncertain effects on a fetus or uncertain efficacy in the setting of an intracardiac foreign body, some AF groups should be excluded from even off-label treatment with ximelagatran at this time, such as pregnant patients and patients with prosthetic heart valves (Table 1). It is hoped that postmarketing clinical trials will be performed in those AF populations most likely to receive ximelagatran off-label, such as those listed here, so that additional important large-scale trial experience will become available.

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Moreover, as for many pharmaceutical agents, pharmacokinetic and safety considerations will also limit the use of ximelagatran. More specifically, some patients might best be excluded from treatment with ximelagatran because of expected uncertainties or concerns regarding dosing or safety monitoring. Accordingly, because monitoring of ximelagatran's effects on hepatic function will be a requirement for its use (see below), this agent should not be given to patients in whom liver function tests cannot be evaluated because of hepatic disease or, perhaps, because of the use of concomitant agents that may confound interpretation of hepatic function tests. Also, because it is a renally excreted agent (see below), ximelagatran should be avoided in patients with advanced or unstable renal disease. Additional exclusions that might be considered by the FDA are those used in the SPORTIF III and V trials as contraindications to both ximelagatran and warfarin, including recent stroke or TIA (in which the risk of creating a hemorrhagic infarct is a concern); acute coronary syndrome (in which many other agents that affect coagulation, in a combined regimen, are presently standards of care); increased risk of bleeding; other contraindications to anticoagulation; recent drug addiction, alcohol abuse, or both; and breast-feeding.

Patients Who Might Switch from Warfarin to Ximelagatran

Patients who are likely to be switched from warfarin to ximelagatran (Table 2) include those who:

- Are noncompliant with prothrombin time testing schedules
- Are unable to achieve and maintain stable International Normalized Ratio (INR) values
- Have experienced or may experience potential food or drug interactions with warfarin
- Have nonbleeding complications on warfarin
- Have a preference for ximelagatran
- Have physicians with a preference for ximelagatran

Because ximelagatran is administered without the need for routine coagulation monitoring,[1-18] it will be the preferred agent in warfarin-treated patients who are unreliable with prothrombin time monitoring schedules or in whom stable INR values in the target range cannot be achieved and maintained because of genetic resistance,[19] bowel disease, dietary factors, concomitant therapeutic drug alterations, or similar factors. Such patients are likely to be switched from warfarin to ximelagatran. Although blood tests will still be required during the therapeutic administration of ximelagatran, such tests will primarily be related to hepatic function testing, which is likely to be intensive only during the first 6 months of therapy and, therefore, to be much reduced as compared with testing during warfarin treatment over the long-term course of administration. Additionally, because a multitude of drugs (both prescription and over the counter) and dietary supplements interact with warfarin whereas ximelagatran has been free of food and drug interactions to date (excluding erythromycin and azithromycin), many patients using "polypharmacy" regimens are likely to be switched from warfarin to ximelagatran. The

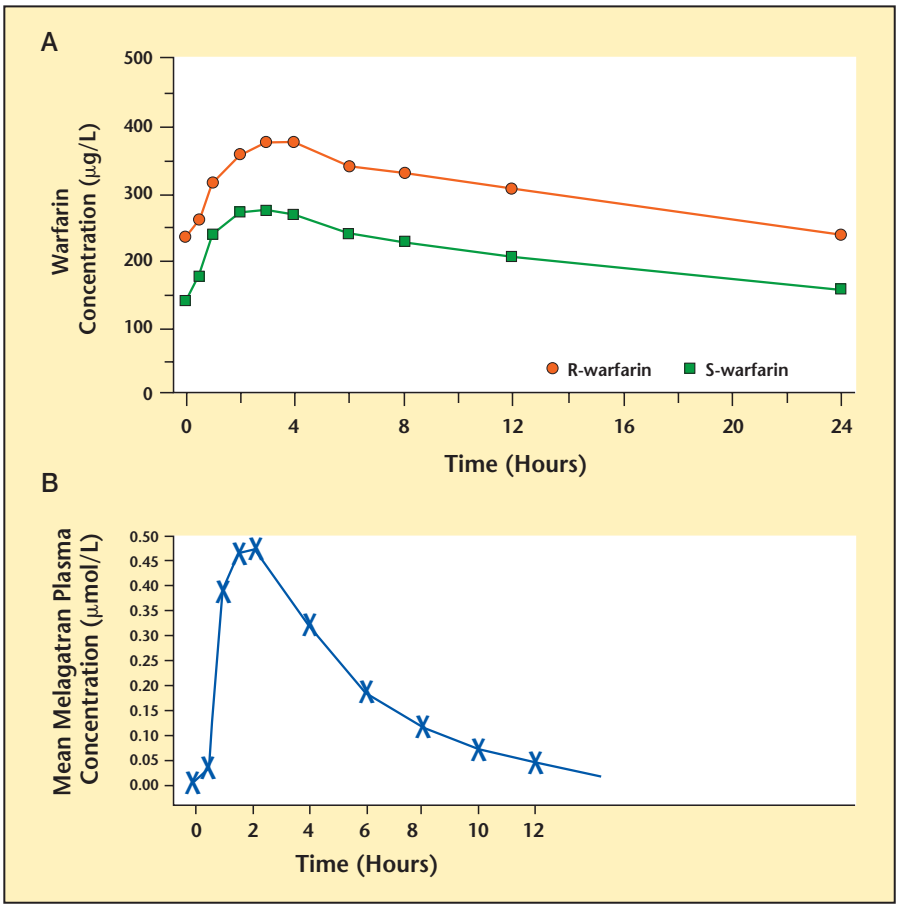

Figure 1. *Pharmacokinetic profiles for standard oral dosing of warfarin* **(A)** *and ximelagatran* **(B)**.

predictable and stable therapeutic levels of ximelagatran in contrast to those of warfarin in such subjects should enhance both ximelagatran's efficacy and safety profile as compared with warfarin in this specific subgroup of patients. Finally, there are rare patients who have experienced nonbleeding complications from warfarin, including serious dermal reactions.[20] Such patients may be given ximelagatran instead. In light of the abovementioned factors, it is likely that many patients, when made aware of the features of ximelagatran—whether by their health care provider or by their own research using the Internet or other resources—will choose to terminate their current therapy with warfarin and be switched to ximelagatran as a preferable alternative. The ability to use a drug with a fixed dosing regimen, no need for coagulation test monitoring, no need for dietary restrictions, and no interaction with the majority of drugs or supplements commonly encountered will be incredibly attractive to most patients in contrast to the lifestyle restrictions imposed by warfarin. For similar reasons, ximelagatran is likely to be more attractive to prescribers as well. An additional benefit for many physicians will be the ability to reduce the size, cost, and burden of running a coagulation monitoring program—as is necessary with warfarin—in which the professional effort is considerable and staff costs are high and generally not reimbursed.

Process(es) Required to Change from Warfarin to Ximelagatran

Transforming a regimen of warfarin to one of ximelagatran will have to be based on the relative pharmacokinetic profiles of these agents. (Figure 1). Elimination of warfarin effect (warfarin washout plus resynthesis of clotting proteins) is slower than attainment of steady state with ximelagatran.[4-6,21,22] The elimination half-life of both S- and R-warfarin has been reported to be as long as 37-53 hours,[21,22] being somewhat variable because of different degrees of genetic sensitivity.[20] In my experience, it takes 48 hours or more for warfarin levels to become significantly subtherapeutic in most patients after discontinuing the agent. In contrast, ximelagatran dosing yields significant activity of melagatran (the active form of the drug) in 2-3 hours.[4-6] Accordingly, and as determined by any sense of urgency, one would have to either accelerate the elimination of warfarin effect or delay the administration of ximelagatran until the INR is nearing the lower therapeutic margin. Thus, the options for changing

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from warfarin to ximelagatran could reasonably include the following:

- All patients: stop warfarin, give vitamin K, start ximelagatran in 12-24 hours.
- Low-risk patients: discontinue warfarin and defer initiating ximelagatran until the risk of bleeding from combined therapeutic actions is presumed low enough, eg, until the INR is <2.0 (using daily INR monitoring), or for an arbitrary period of 3 days (which may depend on the INR value when warfarin is stopped), or whichever comes first.
- High-risk patients: discontinue warfarin, then start ximelagatran after the INR is <2.5 (using daily INR monitoring).

High-risk patients might include those with a prior embolic stroke or SEE, or with multiple other ACCP or ACC/AHA/ESC risk markers.[7,8] The above suggestions are formulated on considerations of minimizing embolic risk upon warfarin discontinuation while minimizing bleeding potential during the period of overlap of the therapeutic agents' actions. They are similar to the considerations one might take into account when transferring a patient from warfarin to LMWH (another family of agents with rapid action and no need for routine coagulation monitoring). Notably, if on approval of ximelagatran by the FDA, the package insert for ximelagatran offers alternative suggestions for transferring patients from warfarin to ximelagatran, they should be strongly considered.

Patients Who Might Be Required to Change from Ximelagatran to Warfarin

Patients who might be required to change from ximelagatran to warfarin include those who develop a contraindication specifically to ximelagatran but not to a strategy of anticoagulation, those who develop a transient change in circumstances in which data or custom might be interpreted as showing a preference for warfarin, and those for whom cost considerations mandate generic warfarin. Progressive renal insufficiency or the unusual patient with persistent significant elevations of hepatic function tests during ximelagatran administration are examples of the first group. Patients who are to undergo elective cardioversion are an example of the second group if the physician involved does not use ximelagatran off-label for anticoagulation during the pre- and postcardioversion periods (approximately 1 month of each) but instead prefers to transfer the patient to warfarin treatment during this period, as warfarin is currently the standard of care peri-cardioversion. Cost issues may become the determining factor for some self-pay patients and also for managed-care patients if ximelagatran is a noncovered agent, as warfarin is fully covered. However, in circumstances in which cost is a factor in choosing an anticoagulant, it is hoped that appropriate consideration is given to the total cost of care, ie, not just the cost of the prescription drug but also the relative cost of the hepatic testing schedule versus INR monitoring (including the laboratory charges themselves as well as the access costs) and the costs of the higher expected total bleeding events with warfarin along with their consequences (as occurred in SPORTIF and the other major ximelagatran-vs-warfarin trials).

How to Change from Ximelagatran to Warfarin

It takes 6-60 hours to inhibit the synthesis of the clotting proteins altered by warfarin, whereas ximelagatran has an anticoagulant effect in 2-5 hours and is at steady state by 24 hours.[4-6,23-25] Its effect is also gone in 24 hours. Consequently, there will need to be some overlap of therapy when transferring a patient from ximelagatran to warfarin, and the overlap may vary with whether or not warfarin loading is utilized. Using the model of overlap with heparin during warfarin loading seems reasonable. That is, begin warfarin before discontinuing xime-

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Table 3
Issues Regarding Ximelagatran That Must Be Considered

Use in new-onset atrial fibrillation
Dose adjustment for renal dysfunction
Temporary interruption of therapy for an invasive procedure
Response to a missed dose
Response during a bleeding event
Drug interactions
Hepatic function testing
Use with aspirin
Assessment of compliance
Response in the event of an embolus

lagatran, and discontinue ximelagatran when the INR approaches or reaches the therapeutic range (using a similar set of values as was discussed above in the section on switching from warfarin to ximelagatran).

Assumption 2: Ximelagatran Receives FDA Approval for Anticoagulation of AF Patients and Is Widely Adopted for Clinical Practice

If ximelagatran is approved by the FDA and is widely accepted by clinicians for the anticoagulation of high-risk AF patients, several additional management issues are likely to become particular concerns for physicians and will have to be addressed (Table 3). These factors include

- The patient with new-onset AF
- Conditions requiring dose adjustments, such as
  - ❍ Temporary interruption of therapy for a procedure
  - ❍ Management during a bleeding episode or following an acute stroke
  - ❍ Change in renal function
  - ❍ Missed doses
  - ❍ Alterations in hepatic function studies
  - ❍ Management in the event of an embolic event

New-Onset AF

The current approach of anticoagulation to new-onset AF is usually dichotomized by a 48-hour window.[8] If AF is known to be less than 48 hours in duration, cardioversion without anticoagulation coverage is generally employed. If, however, the duration of AF is longer than 48 hours or is uncertain, current practice employs either a strategy of anticoagulation before elective cardioversion for a period of at least 3 weeks, during which the INR is consistently >2.0, plus anticoagulation following cardioversion, or a strategy of transesophageal echocardiography (TEE) with immediate cardioversion if atrial thrombus is absent, but delayed cardioversion following anticoagulation, as above, if atrial thrombus is detected.[8] Often during the initiation of warfarin within either of these 2 strategies, heparin or LMWH is utilized.

The availability of ximelagatran, with its rapid onset of action, could alter the approach to new-onset AF if data in this circumstance were available. Recall, however, that SPORTIF enrolled only patients with a chronic AF pattern (persistent AF or recurrent paroxysmal AF), rather than new-onset AF, and that SPORTIF excluded patients who were to undergo elective cardioversion. Nonetheless, if ximelagatran were available for clinical use, it might be used off-label in this setting for new-onset AF of greater than 48 hours duration. Because the onset of action with ximelagatran is almost as rapid as with heparin, if the TEE were negative, one might initiate ximelagatran, cardiovert, then continue on ximelagatran, rather than initiating anticoagulation with a heparinoid plus warfarin, discontinuing the heparin compound when the INR reached 2.0, continuing the warfarin for a month or more, and then finally transferring the therapy to ximelagatran under an FDA-approved indication. The latter is clearly less convenient but is consistent with currently available data, and will remain so until a cardioversion trial is performed with ximelagatran and it demonstrates positive (efficacy) results. Alternatively, but still off-label, for new-onset AF greater than 48 hours, one could initiate therapy with ximelagatran and cardiovert electively in 3 weeks. This is in contrast to the approach of using warfarin without a TEE only in that with warfarin, the INR must be 2.0 or higher for 3 consecutive weeks before cardioversion, which often actually requires 4-6 weeks because of the variability in warfarin requirements and the time it takes to achieve a stable INR value.

With new AF of recognized onset, one could initiate ximelagatran at the onset of symptoms. Full anticoagulation would be achieved within 24 hours. The 48-hour dichotomy period of unanticoagulated AF would become irrelevant for such patients, and cardioversion could then be performed as early as convenient, but would not have to be within the 48-hour window. The role for TEE in such a circumstance would cease to exist. For AF without clear recognition of onset, TEE-guided or delayed cardioversion would still be required.

Conditions Requiring a Dose Adjustment

Temporary interruption of therapy for a procedure. In a patient taking warfarin, when an invasive procedure is to be performed, anticoagulation must be withheld for several days[1,26] so as to eliminate the risk of excessive bleeding were the procedure to be done under anticoagulation conditions. In high-risk patients, heparin coverage is employed during the immediate pre- and postprocedure periods of warfarin washout and reinitiation, holding the heparin only for the relatively short time it takes for elimination of heparin effect (ie, ≤ 12 hours). If ximelagatran were used instead of warfarin, the protocol would be much simpler. Because ximelagatran's effect is gone within 24 hours and its effects begin again approximately 2 hours after reinitiation of therapy, ximelagatran could be held 1 day before the procedure and restarted the night of or the day after the procedure (or when bleeding risk is felt to be acceptable) without the need for heparin coverage and without as long a period of sub-

therapeutic anticoagulation, as would follow warfarin discontinuation in the absence of heparin coverage.

Handling of ximelagatran during a bleeding event. As with any anticoagulant, an acute bleeding event will usually signal the need to interrupt anticoagulation therapy. If the bleed is significant, ideally the anticoagulant effect of the agent being employed would be quickly reversible. Consider the current approach of using vitamin K or fresh frozen plasma (FFP) for warfarin, or protamine for heparin, during such a circumstance. There is no direct "antidote" for ximelagatran. Accordingly, if bleeding occurs in a patient taking ximelagatran, ximelagatran should be discontinued, and the patient supported hemodynamically with transfusion if necessary until drug washout occurs (by 24 hours) and/or the bleeding ceases. FFP may be employed, but because of the relatively large safety margin (see above) with achieved ximelagatran concentrations, FFP may not be effective. Ximelagatran, however, can be removed by dialysis and by charcoal hemofiltration, thus accelerating the termination of its anticoagulant action.[27]

Ximelagatran dosing with renal dysfunction. Because ximelagatran is a renally excreted drug and serum concentrations and effect increase substantially with significantly impaired renal function,[28] patients with a creatinine clearance of < 30 mL/min will require a modified dosing schedule. Possible responses would be to change to a once-a-day dose (ie, 36 mg once instead of twice daily) or to halve the twice-daily dose to 18 mg twice daily. It will be important to examine the package insert for the FDA instructions that are expected to be included regarding this circumstance. This consideration would include not only those with chronic renal disease but those in whom renal function impairment is expected to be transient, as following an angiographic dye reaction. If uncertain as to whether the lower dose is sufficient, one could perform a thrombin time assessment, as thrombin time has a roughly linear correlation to ximelagatran serum concentration. Of note, however, mildly elevated ximelagatran levels may not be a concern for short periods of time if one examines the experience in the ESTEEM trial (Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients After Acute Myocardial Infarction) of ximelagatran in acute coronary syndromes,[16] which used a wider dosing range than that used for AF (in combination with aspirin therapy), without excessive short-term bleeding events or disconcerting hepatic impairment.

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Managing a patient who misses a dose of ximelagatran. One missed dose of ximelagatran does not have to be made up, as the levels attained with the recommended 36 mg twice-daily dosing regimen provide a margin of error that covers 1 missed dose (see section below on assessing dosing compliance). Missing more than 1 dose, however, is associated with loss of adequate anticoagulant effect. In the event of a missed dose, the next dose can be taken early (with the dosing clock then being reset) or can be taken on time; extra doses should be avoided. The same advice would hold for a delayed dose due to travel across multiple time zones; the next dose can be taken either as close to the 12-hour time mark as possible or with a delay of a few hours, in which case the dosing clock must be reset.

Ximelagatran and hepatic dysfunction. In the study by Wahlander and colleagues,[29] the pharmacokinetics of ximelagatran in normal subjects and in liver-impaired patients appeared to be similar; the bioconversion of ximelagatran to melagatran was not altered. Accordingly, except in patients with severe hepatic failure, it is unlikely that a dose adjustment of ximelagatran will be required or that its efficacy will be altered. Nonetheless, after FDA approval of ximelagatran, the clinician would do well to consult the package insert to verify that specific recommendations have not been included during the FDA's review of the total database experience with this agent. Of greater concern is the observation that in some patients (approximately 6%), ximelagatran has been associated with the development of alterations in hepatic function tests, most notably the alanine transaminase (ALT) level.[9-18] Thus, although ximelagatran does not require monitoring of coagulation tests during its administration or dosing adjustment in patients with hepatic dysfunction, it does require monitoring of hepatic function tests during its administration. With the most common dosing regimen used in clinical trials of ximelagatran, 36 mg twice daily, elevations in ALT to 3 times normal have occurred in

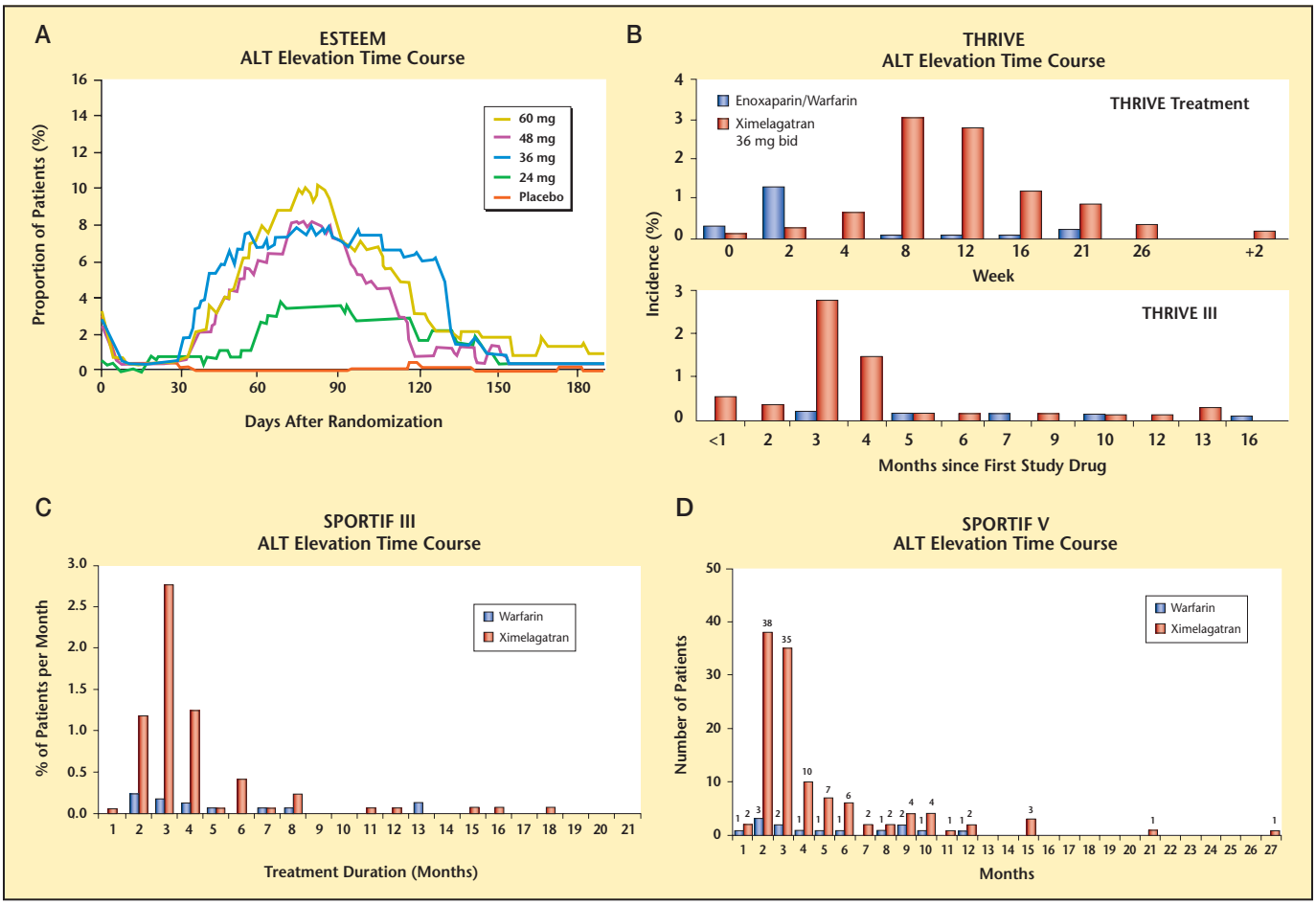

Figure 2. *Effect of antithrombotic agents on liver enzyme levels (alanine aminotransferase [ALT]) as measured in the ESTEEM* **(A)**, *THRIVE* **(B)**, *SPORTIF III* **(C)**, *and SPORTIF V* **(D)** *trials.*

approximately 6% of subjects.[9-18] Elevations to twice normal have occurred in approximately 10% of subjects. (Figure 2). Increases in bilirubin levels have been seen much less frequently (<1%).[9-18] Generally, the increased enzyme levels occur during the first 2-6 months of exposure, and such elevations have usually subsided with or without drug discontinuation.[9-18] For example, in SPORTIF III, in the 1704 patients who received ximelagatran, 107 had elevations of ALT levels to >3 times the upper level of normal. Of 59 patients who were continued on treatment, 55 normalized their levels and 3 returned to less than twice the upper limit of normal. In only 1 patient did the ALT level remain above twice normal, but it had been at this level before enrollment and was at this level after completion of the study. Of the 48 patients in whom ximelagatran was discontinued, 42 normalized their ALT levels and 4 had ALT reductions to less than twice normal. Two patients died from unrelated disorders.[27] Limited data on rechallenge so far suggest events of less frequency and magnitude upon reexposure.[27] In SPORTIF,[9-11] the liver function testing protocol called for (a) baseline liver function testing (enzyme levels above twice normal excluded enrollment); (b) laboratory testing monthly for the first 6 months, then every other month up to 1 year, then every 3 months; (c) if elevation of a hepatic function test was more than 3 times the upper limit of normal, repeat testing weekly until resolution or until determination of alternative cause; (d) discontinuation of ximelagatran per protocol if any level more than 5 times the upper limit of normal was seen or if an increase between 3 and 5 times the upper limit of normal persisted for 8 weeks, or if there was any associated clinical sign of hepatotoxicity. Although what form the final recommendations on the package insert will take is not yet certain, it seems reasonable to assume they will be similar to those used in the clinical trials given that

such guidelines appeared to protect against any clinically important adverse hepatic outcomes. Thus, the clinician who prescribes ximelagatran should consult and follow the recommendations for hepatic function testing that ultimately will be included in the package insert.

Assessing compliance during treatment with ximelagatran. Coagulation tests are not used to monitor ximelagatran dosing or effectiveness. Coagulation tests, however, can be used to assess compliance.[1,4-6,27,30] Thrombin times, activated partial thromboplastin times (APTT), and the activated coagulation time (ACT) are probably the most useful. Thrombin times are almost linearly related to the plasma melagatran concentration. Although the thrombin time is not used for monitoring or to target dosing, it can confirm that the patient has been taking ximelagatran. Thrombin times lower than 100-125 seconds are usually associated with melagatran levels below the minimum effective level of approximately 0.05 μmol/L. The ACT is too sensitive to confirm that a dose has been recent, but it can confirm that ximelagatran has been taken. More specifically, the ACT will begin to become elevated at plasma melagatran concentrations as low as 0.03 μmol/L. At doses of 36 mg twice daily of ximelagatran, serum concentrations of melagatran will almost always remain above the 0.05 μmol/L concentration for almost 24 hours after a dose (see the earlier section on missed doses), and will remain above 0.03 μmol/L for somewhat longer. In contrast, the APTT begins to become elevated at melagatran serum concentrations approximating 0.05 μmol/L. Thus, it should be more than marginally elevated if the last dose has been taken, as the serum level should still be well above the 0.05 μmol/L range.

The clinician who prescribes ximelagatran should consult and follow the recommendations for hepatic function testing that ultimately will be included in the package insert.

Management of ximelagatran in the event of an embolic event. If an AF patient taking ximelagatran suffers an embolic event despite reliability with the regimen, it would be advisable to assess whether the likely source is the left atrium. If so, the options may be either to change to warfarin or to add a second agent. Because crossover was not part of the SPORTIF III or V protocol,[9-11] information as to whether a change to warfarin would provide better protection than continuing the ximelagatran unchanged is lacking. The combination of ximelagatran and aspirin (160 mg) has been used successfully in the acute coronary syndrome protocol ESTEEM,[16] which is being performed as part of the ximelagatran development process. Although total bleeding events with ximelagatran at 36 mg twice daily plus aspirin 160 mg/d were approximately 20% in ESTEEM versus approximately 13% with aspirin alone, the major bleeding event rates were not statistically different (0.7% vs 0.9%). However, anticoagulation in the acute coronary syndrome setting, where the target is coagulation within diseased coronary arteries, may not be an efficacy model for therapy applied to the fibrillat-

Main Points

- If ximelagatran is approved by the Food and Drug Administration (FDA), several issues will have to be addressed, including who will be candidates for ximelagatran therapy, who will not be candidates, what processes will be required to switch patients from warfarin to ximelagatran, and which patients may have to be switched from ximelagatran to warfarin as well as how this transfer will take place.
- If ximelagatran is approved by the FDA and is widely accepted by clinicians for the anticoagulation of high-risk atrial fibrillation (AF) patients, several management issues will need to be addressed, including the approach to treating patients with new-onset AF and the conditions that will require dose adjustments.
- Conditions that may require adjustments to ximelagatran dosing include the temporary interruption of therapy for a surgical procedure, management during a bleeding episode or after an acute stroke, a change in renal function, missed doses, alterations in hepatic function studies, and an embolic event.
- Although current data provide answers to many of the questions concerning ximelagatran therapy, definitive answers to other questions will be found in the package insert material, which is awaiting FDA approval, or in subgroup analyses from the SPORTIF trial, which are not yet available. Therefore, the clinician should diligently follow the medical literature concerning ximelagatran so as to become aware of relevant new information as it becomes available.

ing left atrium. Only the safety data concerning the combination approach would be directly relevant.

If the left ventricle is suspected as the embolic source, the same options as exist for the left atrium would be applicable. In contrast, if the most likely source is felt to be an aortic or carotid plaque, the preferred approach would be the addition of aspirin to the regimen. Recall, however, that if the embolic source is cerebral, it may be necessary to hold ximelagatran dosing for a few days (eg, 48 hours), as is advised by some neurologists for patients anticoagulated with warfarin, to avoid changing the embolic stroke to a more devastating hemorrhagic stroke.

Conclusion

Many clinical questions regarding the use of ximelagatran are anticipated. Current data provide suitable ways to answer many of these questions. Definitive answers to others will require knowledge of the package insert material, which is awaiting FDA approval; subgroup analyses from the SPORTIF database, which are not yet available; or both. As with any newly released pharmaceutical therapeutic agent, the clinician should be diligent in following the medical literature concerning ximelagatran so as to become aware of any relevant material as it becomes available. Finally, despite the great promise of oral thrombin inhibition, there will continue to be a role for warfarin in our treatment armamentarium, albeit a much smaller one. ■

In September 2004, subsequent to the preparation of this manuscript, the Cardiorenal Advisory Committee of the USFDA voted to request additional data concerning ximelagatran, rather than recommend immediate approval. Thus, the information in this article may serve as a guide for the drug's potential future release and as a model of issues to be addressed with the approval of any future anticoagulant.

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