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Hepatic Findings in Long-Term Clinical Trials of Ximelagatran

William M. Lee,[1] *Dominique Larrey*,[2] *Rolf Olsson*,[3] *James H. Lewis*,[4] *Marianne Keisu*,[5] *Laurent Auclert*[5] and *Sunita Sheth*[6]

1 University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA
2 Service Hépato-Gastroentérologie, CHU Montpellier, Hôpital Saint Eloi and INSERM U632, Montpellier, France
3 Sahlgrenska University Hospital, Gothenburg, Sweden
4 Georgetown University Medical Center, Washington, District of Columbia, USA
5 AstraZeneca R&D Mölndal, Mölndal, Sweden
6 AstraZeneca LP, Wilmington, Delaware, USA

Abstract

Objective: In clinical trials, the efficacy and safety of the oral direct thrombin inhibitor ximelagatran have been evaluated in the prevention or treatment of thromboembolic conditions known to have high morbidity and mortality. In these studies, raised aminotransferase levels were observed during long-term use (>35 days). The aim of this analysis is to review the data regarding these hepatic findings in the long-term trials of ximelagatran.

Patients and methods: The prospective analysis included 6948 patients randomised to ximelagatran and 6230 patients randomised to comparator (warfarin, low-molecular weight heparin followed by warfarin or placebo). Of these, 6931 patients received ximelagatran for a mean of 357 days and 6216 patients received comparator for a mean of 389 days. An algorithm was developed for frequent testing of hepatic enzyme levels. A panel of four hepatologists analysed all cases of potential concern with regard to causal relation to ximelagatran treatment using an established evaluation tool (Roussel Uclaf Causality Assessment Method [RUCAM]).

Results: An elevated alanine aminotransferase (ALT) level of >3 × the upper limit of normal (ULN) was found in 7.9% of patients in the ximelagatran group versus 1.2% in the comparator group. The increase in ALT level occurred 1–6 months after initiation of therapy and data were available to confirm recovery of the ALT level to <2 × ULN in 96% of patients, whether they continued to receive ximelagatran or not. There was some variability in the incidence of ALT level elevation between indications, those with simultaneous acute illnesses (acute myocardial infarction or venous thromboembolism) having higher incidences. Combined elevations of ALT level of >3 × ULN and total bilirubin level of >2 × ULN (within 1 month of the ALT elevation), regardless of aetiology, were infrequent, occurring in 37 patients (0.5%) treated with ximelagatran, of whom one sustained a severe hepatic illness that appeared to be resolving when the patient died from a gastrointestinal haemorrhage. No death was observed directly related to hepatic failure caused by ximelagatran.

Conclusion: Treatment with ximelagatran has been associated with mainly asymptomatic elevation of ALT levels in a mean of 7.9% of patients in the long-term clinical trial programme and nearly all of the cases occurred within the

first 6 months of therapy. Rare symptomatic cases have been observed. An algorithm has been developed for testing ALT to ensure appropriate management of patients with elevated ALT levels. Regular ALT testing should allow the clinical benefits of ximelagatran to reach the widest population of patients while minimising the risk of hepatic adverse effects.

Ximelagatran is the first oral direct thrombin inhibitor to reach the market and has been approved for the prevention of venous thromboembolic events after total hip or total knee replacement in 14 countries to date. It is the first new oral anticoagulant since the introduction of the vitamin K antagonist warfarin, almost 60 years ago.

Vitamin K antagonists, the currently available long-term anticoagulants, are very effective antithrombotic agents but take several days to achieve an adequate therapeutic effect, have a variable anticoagulant effect, multiple food and drug interactions, and a narrow therapeutic window.[1-3] This presents a risk of excess thromboembolic events at subtherapeutic anticoagulant levels (below the target international normalised ratio [INR]) or bleeding – sometimes fatal – at supratherapeutic levels. To minimise these risks, frequent monitoring of anticoagulant intensity and subsequent dose adjustment are necessary throughout therapy.[2,3] The difficulties of managing vitamin K antagonist therapy[4] also contribute to their underuse in patients who would benefit from treatment according to evidence-based guidelines. It has been estimated that 50% of patients with atrial fibrillation (AF) with additional stroke risk factors and without contraindications do not receive vitamin K antagonists for stroke prevention because of these concerns.[4,5]

By contrast, oral ximelagatran has the advantages of a rapid onset of action, and a predictable and stable pharmacokinetic and pharmacodynamic profile that allows long-term use in fixed doses without coagulation monitoring or dose adjustment.[6-8] Ximelagatran has shown a comparable efficacy and safety profile for the prevention and treatment of thromboembolic disorders to that of conventional therapy, although with greater ease of administration.[9-15] When assessing the hepatic safety of ximelagatran it is important to remember that the disorders being treated and prevented (venous thromboembolism [VTE] and stroke) carry a high morbidity and mortality that can be substantially reduced by anticoagulant therapy.[16-23]

It is standard practice during clinical trials to monitor hepatic laboratory tests, such as serum aminotransferase, total bilirubin or alkaline phosphatase (ALP) levels, and to investigate their potential clinical significance as indicators of hepatotoxicity should abnormalities occur.[24] No evidence of hepatotoxicity was observed with ximelagatran in preclinical assessments or in short-term use in humans, including the phase III clinical trials for the prevention of VTE (i.e. deep vein thrombosis and/or pulmonary embolism) in elective hip or knee replacement surgery.[25-29] In fact, at the end of the 7- to 12-day prophylaxis period in the combined studies, the incidence of alanine aminotransferase (ALT) level elevations to >3 × the upper limit of normal (ULN) was small (0.91% in the ximelagatran group and 0.70% in the warfarin group) in patients who underwent total knee replacement. ALT level increases were consistently less frequent with ximelagatran than with low-molecular weight heparin (LMWH), evaluated in total hip or total knee replacement.

Increased hepatic enzyme levels were first observed at a higher frequency (4.3%) than in the control group in a study evaluating the long-term use of ximelagatran (>35 days) in comparison with warfarin.[11] Following this initial observation, the frequency of hepatic laboratory testing was increased in all long-term clinical trials of ximelagatran and it was decided that early discontinuation of the study drug should be performed in patients with raised levels of hepatic enzymes in accordance with a pre-specified protocol algorithm.

The aims of this evaluation were as follows: to compile data from the long-term clinical trials programme to characterise the observed increases in ALT levels (the primary signal of an hepatic effect of ximelagatran as well as other drugs); to describe the incidence and time course of the hepatic enzyme level elevations; and to compare the recovery of

ALT levels in patients who stopped and those who continued treatment. In addition, a panel of four hepatologists with expertise in drug-induced hepatic diseases (W.M. Lee, D. Larrey, R. Olsson and J.H. Lewis) evaluated detailed clinical information for cases of potential concern to assess the likelihood of a relationship between hepatic findings and study drug in individual patients. Collectively the evidence has been used to enhance understanding of the clinical consequences of the observed increases in the hepatic enzyme levels.

Methods

Patient Population and Treatments

Patients were included from all studies in which the planned treatment duration was >35 days and the data were examined prospectively. Basic methodology for the individual studies has been published previously.[9-15] The total long-term treatment population consisted of 6948 patients randomised to ximelagatran and 6230 patients randomised to comparators. Four disease-based populations were represented: patients with AF who were undergoing therapy for the prevention of stroke and thromboembolic complications comprised approximately 58% of the total; patients with acute symptomatic deep vein thrombosis with or without pulmonary embolus undergoing treatment of VTE (VTE-T group) represented 19% of the total; patients undergoing long-term secondary prevention of VTE (VTE-P group) made up 9% of the total; and the group in a dose-ranging study of prevention of cardiovascular events in patients with post-acute myocardial infarction (AMI) made up the remaining 14% of the total.

In the AF group, patients were randomised to receive oral ximelagatran or adjusted-dose warfarin in one of four trials: SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation) II,[11] SPORTIF IV[12] or the phase III trials SPORTIF III (open-label)[13] and SPORTIF V (double-blind).[14] Patients in the VTE-T group were randomised to receive ximelagatran or standard therapy with enoxaparin followed by adjusted-dose warfarin for 6 months.[9] In the VTE-P group, patients who had received standard oral anticoagulation for 6 months were randomised to ximelagatran or placebo for 18 months.[10] Patients in the post-AMI pool took part in a 6-month, dose-guiding study in which all dose groups also received aspirin (acetylsalicylic acid) 160mg daily.[15]

Evaluation of Adverse Events

A list of all adverse event symptoms known to be associated with acute hepatitis (viral or drug-induced) was developed[30,31] and these terms were specifically searched for among the adverse events reported by the investigators and were considered to be adverse events 'possibly associated with an hepatic disorder' for the purposes of this analysis.

Hepatic Enzyme Testing and Enhanced Safety Surveillance

During the long-term clinical trials programme for ximelagatran, ALT, aspartate aminotransferase (AST), ALP and total bilirubin levels were routinely measured by a central laboratory from blood samples taken from patients at specified timepoints (usually monthly). Initially, patients with known hepatic disease were excluded and no limits were set for treatment discontinuation. As the programme progressed, the criteria for testing and treatment discontinuation were tightened. The frequency of testing was increased and treatment was discontinued if ALT level elevations exceeded certain thresholds; specifically, a weekly testing routine was initially implemented if the ALT level was >3 × ULN, which was later changed to >2 × ULN, and treatment was discontinued initially if the ALT level was >7 × ULN, which was later changed to >5 × ULN or a persistent level of >3 × ULN for 4 weeks. The ALT testing algorithm in place during the later phase of the long-term clinical trials programme is described in detail in figure 1.

Hepatic enzyme data were obtained from a central laboratory common to all trials, but in order to allow the fullest possible documentation of results, data from local laboratory tests taken outside the clinical trial protocol were also collected. At the time of the cut-off date for inclusion of data in this analysis (27 June 2003 for central laboratory data and 27 March 2004 for local laboratory data), all studies were complete except for SPORTIF IV, a 5-year follow-up of SPORTIF II, which has been

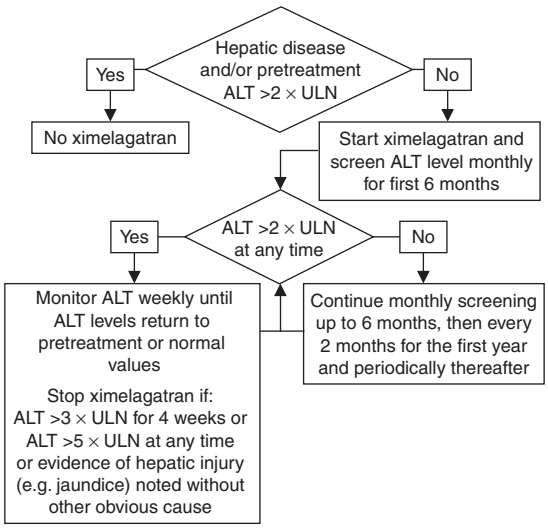


Fig. 1. ALT level testing schedule and management algorithm in place by the end of the long-term clinical trials programme. **ALT** = alanine aminotransferase; **ULN** = upper limit of normal.

ongoing since 30 June 2001 and for which data were available for up to 2 years of follow-up.

In order to ensure appropriate and continuous surveillance, the central laboratory data from all patients were transferred to, and checked monthly by, the central drug safety unit at AstraZeneca. Once the hepatic enzyme data suggested a signal for potential hepatotoxicity, a 4-person data and safety monitoring committee was appointed (during the ongoing phase III trials), composed of hepatologists (W.M. Lee, D. Larrey, R. Olsson and J.H. Lewis) with expertise in drug hepatotoxicity, to review data from past and ongoing studies. Detailed clinical information on patients with elevated hepatic enzyme levels was requested on an ongoing basis by questionnaire and the collection of standard study case report forms. This included: patient history; concomitant drugs; symptoms; results of other tests (such as ultrasound examinations) if performed; a panel of predefined follow-up laboratory investigations (such as specialised hepatitis serologies and measurements of autoantibodies) conducted at the central laboratory; and any additional local laboratory liver enzyme test results available.

Statistical Analysis

Data are presented for the number or percentage of patients who exceeded different multiples of the ULN. All analyses used the central laboratory data as well as local laboratory data. Comparisons between groups for proportions of events were made with Fisher's exact test, adopting a two-sided statistical significance level of 0.05. Linear relationships between continuous variables were assessed with Pearson's product moment correlation coefficient. Potential risk factors that may have contributed to hepatic enzyme level elevation were investigated and analysed by stepwise logistic regression analysis, using the criterion of $p < 0.05$ for factors to be maintained in the final model. Patients who had a combined increase in ALT levels of >3 × ULN and total bilirubin levels of >2 × ULN within 1 month of the ALT elevation were identified and their hepatic results characterised in detail.

Roussel Uclaf Causality Assessment Method (RUCAM)

A standardised method, the 'Roussel Uclaf Causality Assessment Method' (RUCAM),[32,33] was used to assess all hepatic laboratory findings of potential clinical significance. This method is increasingly recommended as the most reliable way to assess the likelihood that hepatic events are related to a specific drug.[34-36] It takes into consideration factors such as age, history of alcohol use, time to onset and course of the reaction, exclusion of non-drug-related causes and concomitant medication, previous information on hepatic reactions to the drug currently being assessed and response to re-administration. A proactive effort was made to collect all necessary data so that RUCAM assessment could be applied. Hepatic reactions were also assessed as being of hepatocellular, cholestatic or mixed type, based on the ratio of ALT over ALP.[37] The RUCAM scores indicate the likelihood of a relationship as follows: ≤0 excluded; 1–2 unlikely; 3–5 possible; 6–8 probable; >8 highly probable. The four hepatologists made individual assessments of the causality in all cases and the mean scores were calculated, hence fractional scores were possible. For this reason, the thresholds in the present analysis (i.e. mean RUCAM scores from the four hepatologists) were set at: ≤0 excluded; >0 to <3 unlikely; ≥3 to <6 possible; ≥6 to ≤8 probable; >8 highly probable. RUCAM is used to determine the causality relationship of a specific drug to an event involving

either hepatocellular or cholestatic hepatic injury and has no relevance to prediction of outcome of non-hepatic events.

Patients were selected for RUCAM assessment if they met any of the following five criteria: ALT >10 × ULN; ALT >3 × ULN and total bilirubin >1.5 × ULN; patients who died at any time after having developed ALT >3 × ULN; patients with first ALT >3 × ULN after 6 months of therapy; patients who had total bilirubin >3 × ULN. Note that the threshold of ALT >3 × ULN combined with total bilirubin >1.5 × ULN, used for the selection of patients in this analysis, is included in the original criteria cited in the first US FDA Clinical White Paper to identify cases of potential concern, whereas the updated White Paper states a higher threshold of ALT >3 × ULN combined with total bilirubin level of >2 × ULN.[24]

Results

Patients and Duration of Exposure to Study Drug

The analysis of hepatic enzyme levels used the intention-to-treat population, which consists of 6948 patients randomised to ximelagatran and 6230 patients randomised to comparators (active or placebo). The two groups were well balanced for demographic characteristics. Approximately 65% were aged ≥65 years and 30% were aged ≥75 years, the age range was 18–97 years and 64% were men.

The overall mean duration of treatment per patient was approximately 1 year. Specifically, among patients who received at least one dose of the study drug or placebo, and for whom data were available (i.e. the 'safety population'), the mean duration was 357 days (standard deviation [SD] 231 days) for 6931 patients in the ximelagatran group and 389 days (SD 223 days) for 6216 patients in the comparator group. The slightly shorter mean duration in the ximelagatran versus the comparator group reflected the mandated discontinuations of study drug associated with specified ALT level elevations. The mean durations of treatment with ximelagatran in the individual patient groups were AF 480 days, VTE-T 154 days, VTE-P 445 days and post-AMI 136 days. The total number of ximelagatran patients for whom ALT level measurements were available at different timepoints after the start of treatment were: >0 months 6841 (representing the number of patients having ALT measurements up to and including 1 month, the difference between this and the total intention-to-treat population being due to the number of patients not receiving drug or not having a sample taken within 1 month); >3 months 6221; >6 months 5648; >12 months 3569; >18 months 2127; >24 months 404.

Symptoms and Adverse Event Terms Possibly Associated with an Hepatic Disorder

An analysis in the ximelagatran clinical trial programme showed no difference in the number of adverse events 'possibly associated with an hepatic disorder' between the ximelagatran-treated patients (1402 of 6931; 20.2%) and patients receiving a comparator (1192 of 6216; 19.2%). When analysing the trials individually, no differences were seen between the ximelagatran and comparator groups except in the open-label study in patients with AF (SPORTIF III). This showed a statistically significant difference ($p = 0.0028$) in the incidence of adverse events 'possibly associated with an hepatic disorder' between treatments, which favoured warfarin: 307 of 1698 patients (18.1%) in the ximelagatran group versus 242 of 1699 patients (14.2%) in the warfarin group. The adverse events that were more common in the ximelagatran group than in the comparator group in this study were non-specific, namely fatigue, nausea, abdominal pain, dyspepsia and flatulence.

As expected, in both the ximelagatran and comparator groups, patients with ALT levels of >3 × ULN had a higher incidence of adverse events 'possibly associated with an hepatic disorder' than those without ALT level elevation. The respective incidences were 25.5% versus 19.7% for ximelagatran and 25.3% versus 19.0% for comparators. Of the adverse events that occurred in ≥1% of patients in the ximelagatran or comparator groups (with or without ALT level elevation), the apparent differences between the patients with elevation versus those without elevation were mostly in non-specific symptoms such as nausea, abdominal pain and fatigue. Thus, in the ximelagatran treatment group, symptoms and adverse events such as nausea (8.8%

vs 4.7%), fatigue (7.3% vs 5.9%), dyspepsia (4.4% vs 3.5%), 'hepatitis' (1.1% vs <0.1%) and jaundice (1.1% vs <0.1%) were >20% more frequent among patients with ALT levels of >3 × ULN (n = 546) than in those without this elevation (n = 6385). In the comparator group, abdominal pain (9.3% vs 4.2%), nausea (9.3% vs 4.9%), vomiting (6.7% vs 2.1%), dyspepsia (4.0% vs 3.0%), 'hepatitis' (1.3% vs <0.1%) and jaundice (1.3% vs 0.1%) were >20% more frequent among patients with ALT levels of >3 × ULN (n = 75) than in those without this elevation (n = 6141); fatigue was less frequent (1.3% vs 6.0%).

Incidence of Elevations of ALT and Other Hepatic Tests

Frequency of Elevations in the Long-Term Treatment Population

In the overall long-term treatment population, an increase in ALT levels of >3 × ULN was observed in 546 patients (7.9%) in the ximelagatran group versus 75 patients (1.2%) in the comparator group (placebo, warfarin, or LMWH followed by warfarin) [table I]. Although there was a strong correlation between the incidence of ALT elevations to various multiples of ULN and elevations of AST to corresponding levels ($r = 0.72$; $p < 0.0001$), the incidence of AST level elevations was generally lower. Few patients had elevations in ALP or total bilirubin levels of >2 × ULN and the incidences were similar for both the ximelagatran and the comparator group (table I).

Table I. Incidence of patients [n (%)] with elevated ALT, AST, ALP and/or total bilirubin levels in the overall long-term exposure population[a] for ximelagatran versus comparator agents

Hepatic enzyme test	Ximelagatran (n = 6948)	Comparator (n = 6230)
ALT		
>2 × ULN	860 (12.4)	192 (3.1)
>3 × ULN	546 (7.9)	75 (1.2)
>5 × ULN	328 (4.7)	29 (0.5)
>10 × ULN	132 (1.9)	5 (0.1)
AST		
>2 × ULN	555 (8.0)	109 (1.7)
>3 × ULN	354 (5.1)	50 (0.8)
>5 × ULN	194 (2.8)	23 (0.4)
>10 × ULN	72 (1.0)	5 (0.1)
ALP		
>2 × ULN	138 (2.0)	66 (1.1)
>3 × ULN	47 (0.7)	22 (0.4)
Total bilirubin		
>1.5 × ULN	282 (4.1)	224 (3.6)
>2 × ULN	86 (1.2)	66 (1.1)
>3 × ULN	41 (0.6)	16 (0.3)
>5 × ULN	20 (0.3)	7 (0.1)

a Combined AF, VTE-T, VTE-P and post-AMI patient groups.

AF = atrial fibrillation; **ALP** = alkaline phosphatase; **ALT** = alanine aminotransferase; **AMI** = acute myocardial infarction; **AST** = aspartate aminotransferase; **ULN** = upper limit of normal; **VTE-P** = secondary prevention of venous thromboembolism; **VTE-T** = treatment of acute venous thromboembolism.

Frequency of ALT Elevations in Individual Studies and Disease Groups

In a comparison of the different patient populations, the incidence of ALT levels of >3 × ULN was 6.2% in the AF group (mostly ximelagatran 36mg twice daily) and 6.0% in the VTE-P group (ximelagatran 24mg twice daily). Somewhat higher incidences of ALT levels of >3 × ULN were seen in patients in the VTE-T group (10.2%), who received ximelagatran 36mg twice daily and in patients in the higher-dose groups of the phase II dose-guiding study for post-AMI (ximelagatran plus aspirin; 6.5% of patients receiving ximelagatran 24mg twice daily and 12.2–13.2% of patients receiving 36–60mg twice daily). Overall, a dose-response relationship could not be established. There was also some variation in the incidences of ALT levels of >3 × ULN in the comparator groups. A slightly higher incidence (2.0%) was seen in the VTE-T group, who were treated with enoxaparin followed by warfarin, than in the others: AF (warfarin) 0.8%, VTE-P (placebo) 1.0% and post-AMI (placebo plus aspirin) 1.3%.

Time to Initial ALT Elevation

Data were analysed to evaluate the time course of the first occurrence of an increase in the levels of ALT (figure 2). Of the 546 ximelagatran-treated patients with ALT levels of >3 × ULN, 93% occurred within the first 6 months and 98% within the first 12 months.

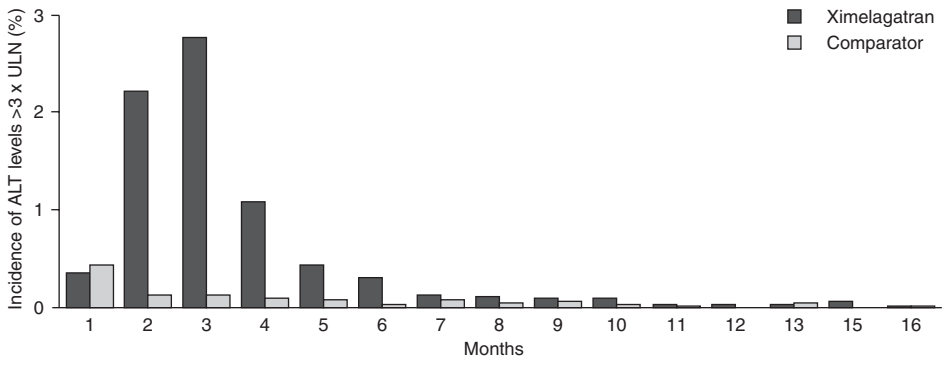
Recovery of ALT Levels Towards Normal

For the analysis of recovery of raised ALT levels, elevated ALT levels (>3 × ULN) that subsequently fell to <2 × ULN were considered to have returned

towards normal, on the basis that a number of investigators stopped follow-up below this threshold because they considered levels of <2 × ULN to represent a satisfactory resolution. Of the 546 patients in the ximelagatran group who had ALT levels of >3 × ULN, 96% were documented to have returned to ALT levels of <2 × ULN. In fact, most (84%) had a documented post-elevation ALT level of ≤1 × ULN (table II). Among the 75 comparator patients with ALT levels of >3 × ULN, 93% were documented to have returned to <2 × ULN by the end of the study. Further information on the ximelagatran patients is provided in the following sections. Less effort was made to follow-up the comparator patients after the end of the studies.

Subdividing the recovery data according to whether patients were still receiving or had discontinued ximelagatran treatment during the period after the elevated ALT level (table II), ALT levels returned to <2 × ULN in 318 of 342 patients (93%) who discontinued ximelagatran. Furthermore, the return of ALT to the same level was documented in all of the 204 patients who continued treatment with ximelagatran after the ALT elevation (table II). The proportions of patients with the higher peak ALT levels during treatment (>5 × ULN or >10 × ULN) were smaller among those who continued to receive ximelagatran than among the patients who stopped receiving the drug, which reflects how the ALT testing algorithm influenced discontinuation at higher ALT levels. The median time to recovery was 30 days in those who were maintained on ximelagatran and 52 days in those who stopped receiving the drug treatment; however, the groups were not comparable because of differences in their peak ALT levels.

Of the 24 ximelagatran-treated patients (4%) in whom ALT levels did not return to <2 × ULN after an elevation, 11 died before their ALT levels normalised. The cause of death was non-hepatic in ten of these patients: four cardiac events, one stroke, one pulmonary embolism, one gastrointestinal (GI) bleeding, one neoplasm, one renal failure/sepsis and one multiorgan failure following operation of colon carcinoma and liver metastases. The other patient died from reactivation of viral hepatitis B. Thirteen patients were alive at last follow-up: six had an alternative explanation for the raised ALT levels (alcohol in three patients, cardiac ischaemia in two patients, hepatitis C in one patient) and seven did not have documented ALT measurements showing recovery. However, available clinical information suggested that none of these seven patients had evidence of ongoing hepatitis after their peak ALT level and discontinuation of ximelagatran.



No. of patients at risk

Months	0	3	6	9	12	15
Ximelagatran	6948	6581	5987	3984	3897	3630
Comparator	6230	6019	5774	4074	3989	3696

Fig. 2. Histogram of the number of patients with ALT levels of >3 × ULN for the first time per month in each treatment group. **ALT** = alanine aminotransferase; **ULN** = upper limit of normal.

Table II. Number of patients out of a total of 546 ximelagatran-treated patients who recovered or did not recover from elevated ALT levels, divided according to whether the patients were on or off ximelagatran treatment during the 'recovery' period after the raised ALT level

Maximum ALT level[a]	Total	Continued taking the drug (n = 204)		Stopped taking the drug (n = 342)			
		204 recovered: ALT level at recovery		318 recovered: ALT level at recovery		24 not recovered: last recorded ALT level	
		≤1 × ULN	1–2 × ULN	≤1 × ULN	1–2 × ULN	2–3 × ULN	>3 × ULN
>3 × ULN	218	120	13	63	12	4	6
>5 × ULN	197	48	5	120	18	1	5
>10 × ULN	131	17	1	93	12	0	8
Total	**546**	**185**	**19**	**276**	**42**	**5**	**19**

a Note that the current algorithm for stopping treatment if ALT reaches >5 × ULN or a persistent level of >3 × ULN was developed during the clinical trials programme, hence patients with higher ALT levels earlier in the programme could continue treatment.

ALT = alanine aminotransferase; **ULN** = upper limit of normal.

Reintroduction After Temporary Discontinuation of Ximelagatran

Overall, 18 patients who had an ALT level of >3 × ULN and discontinued ximelagatran treatment temporarily, subsequently resumed treatment. The duration of re-exposure was >2 months in 16 of the 18 patients and >6 months in 13 of the 18 patients; enzyme levels were measured at least monthly during re-exposure. Of the 18 patients, 17 had no further ALT elevation. One patient had a recurrence of ALT elevation after reintroduction. In this patient, ximelagatran was first discontinued due to an ALT value of 10.3 × ULN with no symptoms. Following reintroduction after 65 days off ximelagatran treatment, a second ALT level elevation to 3.0 × ULN occurred after 2 months. Although this second episode was milder than the original one, the decision was made to stop treatment with ximelagatran permanently. There were no signs or symptoms of hypersensitivity (no fever, rash or eosinophilia) and all hepatic enzyme levels in this patient normalised.

Potential Risk Factors for ALT Level Elevation

The potential factors that may have contributed to hepatic enzyme level elevation were investigated and commonly known risk factors for hepatotoxicity, i.e. age, sex, body mass index, concomitant medications, type of disease treated and race, were integrated. The most significant factor in this analysis was ximelagatran treatment (odds ratio 6.8). Other factors that demonstrated statistical significance all had an odds ratio of <2. Patients post-AMI, patients being treated for an acute venous thromboembolic event, body mass index <25 kg/m^2 and female gender had an increased risk with an odds ratio of <2; Asian patients had a decreased risk with an odds ratio of >0.5 (table III). An association with the use of HMG-CoA reductase inhibitors (statins) or aspirin or the presence of a decreased creatinine clearance level was not identified as significant in this model.

Concurrent Elevations of ALT and Total Bilirubin Levels

Concurrent elevations of ALT 3 × ULN and total bilirubin >2 × ULN in the absence of other explanations (such as cholestasis), i.e. in patients with a hepatocellular type of liver damage that is possibly or probably drug-induced, has been proposed by the FDA to represent a potential indicator of a more severe hepatic effect.[24] Regardless of the aetiology, a total of 37 patients (0.5%) in the ximelagatran group had an ALT level of >3 × ULN and also had an increase in bilirubin level of >2 × ULN within 1 month of the elevated ALT. Five patients (0.1%) receiving the comparator showed these concurrent elevations. However, 26 of the ximelagatran patients had an alternative diagnosis associated with ALT and/or bilirubin level elevation that was other than a drug-induced effect (see table IV).

The treatment course and individual outcomes of all 37 ximelagatran-treated patients and 5 comparator patients with concurrent ALT and bilirubin elevation are provided in table IV. The following summarises these results according to whether or not patients had an alternative liver-related diagnosis to explain both their rise in ALT level and the bilirubin elevation. Of the 26 patients with an alternative associated diagnosis, 14 were off the study drug

after their elevation and recovered to an ALT level of <2 × ULN, whereas 6 were off the study drug and died, either without documented recovery or shortly after drug cessation (1 right-sided heart failure, 1 pancreatic tumour, 1 pulmonary embolism with gastric carcinoma, 1 massive GI bleeding [see Appendix, patient 2], 1 fulminant hepatitis B [see Appendix, patient 3], 1 multi-organ failure following surgery for colon carcinoma and liver metastases). The 6 other patients with an alternative diagnosis continued treatment and their ALT levels improved to <2 × ULN; however, 2 of them died later (1 cardiogenic shock, 1 cardiac arrest). Of the 11 patients with no alternative explanation for elevated ALT and bilirubin levels, 10 were taken off the treatment and recovered, including 1 who had been off the treatment and died without a full recovery (bleeding duodenal ulcer [see Appendix, patient 1]). The other patient continued treatment and recovered.

RUCAM Assessments

A total of 233 patients were evaluated by the RUCAM method; 198 in the ximelagatran group and 35 in the comparator group (25 assigned to enoxaparin/warfarin and 10 to placebo) (table V). In the ximelagatran group, 150 patients (76%) were judged to have a hepatocellular pattern of hepatic enzyme level elevation and 48 (24%) a cholestatic or mixed type. The distribution in the comparator group was 15 patients (43%) hepatocellular and 20 (57%) cholestatic or mixed. The RUCAM assessments are shown in table VI. In the ximelagatran group, 128 cases (65%) were judged to have a 'possible' or 'probable' causality, while 3 cases (9%) in the comparator group had such an assessment. Most – 113 of 128 patients (88%) – of these 'possible/probable' ximelagatran cases were of the hepatocellular type.

For the 37 patients in the ximelagatran group and 5 patients in the comparator group who had a combination of ALT >3 × ULN and total bilirubin >2 × ULN, the RUCAM scores and interpretations for individual patients are presented in table IV. According to the RUCAM assessment, 9 of these 37 patients were believed to have an ALT level elevation 'probably related' to ximelagatran (RUCAM score 6–8). ALT levels recovered towards normal (<2 × ULN) in all of them. The eight patients in table IV meeting the above criteria with a 'possible' diagnosis (RUCAM score ≥3 to <6) included two with alternate diagnoses likely and two who died of other causes, but the deaths were deemed to be indirectly related to the study drug.

The RUCAM data for all 22 ximelagatran-treated patients who had ALT levels of >3 × ULN and who died (see section 2.10) are described in table VII. Nine of these patients also appear in table IV as they had concurrent ALT and bilirubin level elevations.

Mortality in the Ximelagatran and Comparator Groups

All-cause mortality in the total long-term treatment population was similar between the ximelagatran and comparator groups (270 of 6948 patients [3.9%] vs 274 of 6230 patients [4.4%], respectively). The percentage of ximelagatran-treated patients with ALT levels of >3 × ULN who subsequently died did not differ compared with the percentage of those with ALT levels of ≤3 × ULN who died, either in the overall study population (4.0% vs 3.9%) or within each of the separate patient pools (potential indications). The 22 ximelagatran-treated patients with elevated ALT levels who died at any time after they developed ALT levels of >3 × ULN (22 of 546 patients [4.0%]) and the 4 patients who received comparator treatment and had an ALT level of >3 × ULN and subsequently died (4 of 75 [5.3%]) are

Table III. Analysis of potential prognostic factors for ALT level of >3 × ULN, using a stepwise model selection algorithm

Factor[a]	Odds ratio	95% CI
Treatment: ximelagatran vs comparator	6.8	5.3, 8.7
Post-AMI	1.8	1.5, 2.2
Acute VTE	1.7	1.4, 2.1
Body mass index <25 kg/m^2	1.4	1.2, 1.7
Female gender	1.3	1.1, 1.6
Asian race[b]	0.5	0.3, 0.9

a The following variables were included in the model: gender (female); age ≥75 years; weight <50kg; body mass index <25 kg/m^2; creatinine clearance <50 mL/min; Asian race; aspirin (acetylsalicylic acid) use; HMG-CoA reductase inhibitor (statin) use; post-AMI; acute VTE; and secondary prevention of VTE.

b The subgroup of Asian race represented 4% of the total population.

ALT = alanine aminotransferase; **AMI** = acute myocardial infarction; **ULN** = upper limit of normal; **VTE** = venous thromboembolism.

Table IV. Outcomes, alternative diagnoses and RUCAM assessments of the 37 ximelagatran-treated and 5 comparator-treated patients with concomitant elevations of ALT levels of >3 × ULN and total bilirubin levels of >2 × ULN

Age (years); gender	Patient group	Study drug and dose (mg)[a]	Time to ALT level of >3 × ULN (days)	Maximum ALT level (× ULN)[b]	Maximum bilirubin level (× ULN)	Type of reaction	Recovery period on/ off drug	Outcome[c]	Alternative diagnosis to ALT and bilirubin level rise/ comment	RUCAM score[d]
55; m	Post-AMI	X 60	57	20.74	5.82	H	Off	Recovered	No alternative diagnosis	7.25
75; f	AF	X 36	90	9.94	2.05	H	Off	Recovered	No alternative diagnosis, died from aortic rupture 5 months after normalisation	7
71; m	AF	X 36	7	8.63	5.77	M	Off	Recovered	Hospitalised for stroke. Gallstones on echography	6.5
74; m	AF	X 36	92	6.98	2.09	H	Off	Recovered	Total bilirubin elevated throughout the study, possible Gilbert's syndrome explaining a coincidental concomitant bilirubin rise	6.5
72; m	Post-AMI	X 36	34	13.33	6.12	C	Off	Recovered	Probably biliary obstruction, according to the investigator	6.5
81; f	AF	X 36	63	19.38	2.08	H	Off	Recovered	Gallstones on ultrasound	6.25
85; m	AF	X 36	56	12.48	2.23	M	Off	Recovered	No alternative diagnosis	6
82; m	AF	X 36	33	6.69	7.08	C/M	Off	Recovered	No alternative diagnosis, hepatomegaly on echography.	6
78; m	Post-AMI	X 48	58	26.63	5.73	H	Off	Recovered	No alternative diagnosis	6
63; f	VTE-T	X 36	35	4.75	4.55	M	On	Recovered	History of breast cancer, ultrasound showed 'hepatic diffuse disease', normalised while study drug continued	5.5
69; f	Post-AMI	X 60	95	19.00	11.97	H	Off	Recovered	No alternative diagnosis, elevated α-fetoprotein levels, but ultrasound and CT did not reveal any neoplasm	5.25
80; m	AF	X 36	85	30.00	6.92	H	Off	Died,[e] no recovery	No alternative diagnosis to ALT/bilirubin level rise and hepatic necrosis, died from bleeding duodenal ulcer (see Appendix, patient 1)	4.5
75; f	VTE-T	X 36	59	9.50	3.09	H	Off	Recovered	No alternative diagnosis	4.5
73; f	AF	X 36	42	32.96	6.46	H	Off	Recovered	Haematuria and positive faecal occult blood test with anaemia and hypotension, hepatic ischaemia suspected to have contributed to elevated liver enzyme levels	4
62; m	AF	X 36	619	7.65	2.92	H	Off	Recovered	Total bilirubin level elevated throughout the study; possible Gilbert's syndrome explaining a coincidental concomitant bilirubin rise	3.75
80; f	AF	X 36	63	15.19	10.82	H	Off	Recovered	No alternative diagnosis, AST level higher than ALT level throughout the study	3.75
77; m	AF	X 36	63	4.50	9.40	M	Off	Recovered before death[e]	No alternative diagnosis for ALT level rise, died from massive GI bleeding, bilirubin level elevation (half unconjugated) after massive transfusions (see Appendix, patient 2)	3.75

Continued next page

Table IV. Contd

Age (years); gender	Patient group	Study drug and dose (mg)[a]	Time to ALT level of >3 × ULN (days)	Maximum ALT level (× ULN)[b]	Maximum bilirubin level (× ULN)	Type of reaction	Recovery period on/ off drug	Outcome[c]	Alternative diagnosis to ALT and bilirubin level rise/ comment	RUCAM score[d]
80; m	AF	Warfarin	232	5.77	3.41	M	On	Recovered	No alternative diagnosis	2.75
75; m	AF	X 36	158	16.83	5.80	H	Off	Recovered	Concomitant treatment with an HMG-CoA reductase inhibitor. Gallstones. Reported as possible acute biliary obstruction	2.5
78; m	AF	X 36	821	5.54	3.15	M	Off	Recovered	No alternative diagnosis, abdominal scan revealed renal cell carcinoma	2.25
85; m	AF	X 36	22	3.75	5.10	C/M	Off	Recovered	Dilated bile ducts, passing gallstone suspected, sphincterotomy performed	2
71; m	AF	X 36	218	45.52	3.02	H	Off	Recovered	Episode of severe heart failure	1.5
81; m	AF	X 36	115	4.69	7.20	C	Off	Recovered	Gallstone pancreatitis, cholecystectomy performed, bilirubin level elevated throughout study	1.25
72; m	Post-AMI	X 24	28	4.06	3.41	C	On	Recovered	No alternative diagnosis, renal cyst on ultrasound	1.25
65; f	Post-AMI	X 48	12	54.03	2.95	H	Off	Recovered	Right-sided heart failure and alcohol, study medication only taken for 2 days	1.25
59; m	Post-AMI	X 60	57	16.40	7.59	C/M	Off	Recovered	Cyst in the head of pancreas, biopsy during cholecystectomy showed chronic cholecystitis and indurative pancreatitis	1.25
73; m	AF	X 36	60	4.35	9.75	C/M	Off	Recovered	Intrahepatic cholestasis due to flucloxacillin, ximelagatran restarted uneventfully	1
57; m	AF	X 36	228	3.12	2.50	H	Off	Recovered	Dengue fever and sepsis	1
74; m	AF	X 36	46	9.33	7.20	C	Off	Recovered	Carcinoid tumour with metastases to liver, peak ALT level at the time of GI bleeding	0.25
90; m	Post-AMI	X 24	132	4.42	2.23	C	Off	Died,[e] no recovery	Right-sided heart failure, also cause of death	0.25
59; m	Post-AMI	Placebo	6	16.13	7.95	M	Off	Not recovered	Jaundice after 12 days on study drug, inoperable pancreatic tumour	0.25
78; m	AF	Warfarin	128	3.71	6.77	C	Off	Died,[e] no recovery	Pancreatic cancer	0
73; f	AF	Warfarin	278	6.00	3.39	H	On	Recovered	Suspected stone in the common bile duct	0
37; f	VTE-T	Warfarin	14	3.25	2.14	H	On	Recovered	Total bilirubin level elevated throughout the study (possible Gilbert's syndrome explaining a coincidental concomitant bilirubin level rise), ALT level elevation during initial exposure to enoxaparin	0
45; m	AF	X 36	190	4.81	2.77	M	On	Recovered before death[e]	Right-sided heart failure, liver steatosis, died from cardiogenic shock	−0.25

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Table IV. Contd

Age (years); gender	Patient group	Study drug and dose (mg)[a]	Time to ALT level of >3 × ULN (days)	Maximum ALT level (× ULN)[b]	Maximum bilirubin level (× ULN)	Type of reaction	Recovery period on/ off drug	Outcome[c]	Alternative diagnosis to ALT and bilirubin level rise/ comment	RUCAM score[d]
51; m	Post-AMI	X 60	27	11.81	12.86	H	Off	Died,[e] no recovery	Died from pancreatic tumour	−0.25
69; m	AF	X 36	237	3.56	5.00	C	Off	Died,[e] no recovery	Hepatic metastases from gastric carcinoma, died from pulmonary embolism	−0.75
73; m	VTE-T	X 36	9	14.80	3.64	H	Off	Died,[e] no recovery	Reactivation of hepatitis B diagnosed after 18 days on study drug, elevated liver enzymes at baseline, died from fulminant hepatitis (see Appendix, patient 3)	−0.75
66; m	AF	X 36	285	18.40	2.09	H	On	Recovered before death[e]	Right upper quadrant pain and severe heart failure at peak, died 5 months later with abdominal pain, cholecystitis and heart failure, very steep increase and decrease of aminotransferase levels together with a history of hepatic failure the same day are consistent with ischaemic liver	−1
76; m	AF	X 36	179	50.45	6.68	H	On	Recovered	Increase in ALT and bilirubin levels started during exacerbation of psoriasis that was ascribed to concomitant treatment with nebivolol, soon thereafter suspected spontaneous discharge of common bile duct stone, recovered after sphincterotomy, serology showed chronic hepatitis C	−1.5
76; m	VTE-T	X 36	144	25.64	3.03	H	Off	Died,[e] no recovery	Operated for colon carcinoma with metastases to the right liver lobe, post-operative multiorgan failure with fatal outcome	−2
72; m	AF	X 36	232	11.86	4.70	H	On	Recovered	Gallstone, endoscopic retrograde cholangiopancreatography with papillotomy: hepatocellular reaction but also >50% increase in ALP level	−3

a Ximelagatran doses were twice-daily.

b Note that the algorithm for stopping treatment if ALT level reaches >5 × ULN or a persistent level of >3 × ULN was developed during the clinical trials programme, hence patients with higher ALT levels earlier in the programme could continue treatment.

c 'Recovered' = ALT recovered to <2 × ULN; patients who died (with or without recovery of ALT levels) are also indicated in this column.

d Individually assigned RUCAM scores indicate the likelihood of a relationship between study drug and the hepatic test results as follows: ≤0 excluded; 1–2 unlikely; 3–5 possible; 6–8 probable; >8 highly probable. Note that thresholds in the present analysis (i.e. mean RUCAM scores from four hepatologists) were set at ≤0 excluded; >0 to <3 unlikely; ≥3 to <6 possible; ≥6 to ≤8 probable.

e The 9 ximelagatran-treated and 1 comparator-treated patients listed in this table who died after an ALT >3 × ULN are also listed in table VII.

AF = atrial fibrillation; **ALP** = alkaline phosphatase; **ALT** = alanine aminotransferase; **AMI** = acute myocardial infarction; **C** = cholestatic; **CT** = computed tomography; **GI** = gastrointestinal; **H** = hepatocellular; **M** = mixed; **RUCAM** = Roussel Uclaf Causality Assessment Method; **ULN** = upper limit of normal; **VTE-T** = treatment of acute venous thromboembolism; **X** = ximelagatran.

described in table VII. Three of these patients warrant special attention and their details are given in Appendix (patients 1–3). Patient 1 developed signs of hepatic failure with biopsy-proven hepatic necrosis, but subsequently died following GI haemorrhage. Patient 2 died from massive GI haemorrhage, while he had a rise in ALT level and had missed a laboratory check; the role of liver injury as part of his final illness is unclear because of his having concomitant hypotension and massive transfusions with an increasing and decreasing pattern of aminotransferase levels suggestive of ischaemic liver damage. Patient 3 had a reactivation of hepatitis B in the setting of immunosuppressive therapy, with a fulminant course.

Discussion

Ximelagatran has proven to be as effective and well tolerated as comparator anticoagulants in clinical trials in patients at risk of serious thromboembolic diseases.[9,10,13,14,25,26,28,29] Oral ximelagatran has been used in fixed doses without coagulation monitoring or dose adjustment. Owing to the difficulties in optimally managing vitamin K antagonist therapy, the effectiveness and safety of these agents in routine clinical practice are expected to be worse than in clinical trials, which would lead to an excess of thromboembolic and haemorrhagic events compared with optimally managed therapy.[38] Warfarin is one of the leading causes of hospital admissions due to adverse drug reactions[39] and may result in fatal bleeding in 0.6% of patients receiving the drug per year.[40] In addition, vitamin K antagonists are routinely underused in patients who would benefit from anticoagulant therapy.[4,5,41] Such factors must be considered when comparing the overall benefit/risk profile of anticoagulants.

In the final analysis of data from the long-term treatment studies of ximelagatran, ALT level elevation to >3 × ULN was found in 7.9% of ximelagatran-treated patients overall during an average exposure to the drug of approximately 1 year. Overall, the time pattern of ALT elevations was consistent, with most beginning between 1 and 6 months after the start of ximelagatran treatment and few occurring after 6 months. In almost all patients, ALT levels returned towards normal. Importantly, no cases of hepatic failure have occurred in patients compliant with the revised recommended testing implemented in the trial programme.

The laboratory pattern seen with ximelagatran follows the usual hepatocellular type of injury seen with drug-induced hepatic disease, in which there is a predominant increase in ALT and AST levels, whereas a predominantly raised ALP level characterises the less frequent cholestatic syndromes.[37,42] The elevations in ALT levels in the ximelagatran long-term studies were not generally associated with specific clinical symptoms. Although patients with ALT levels of >3 × ULN had a higher frequency of adverse events 'possibly related to an hepatic disorder' than those without ALT level elevation, these results may have been a consequence of the fact that a patient with elevated ALT levels was more often asked about symptoms, a potential bias that might also have been amplified in the open-label SPORTIF III trial. A higher incidence of adverse events 'possibly related to an hepatic disorder' in the ximelagatran versus the warfarin treatment groups in SPORTIF III was not seen in SPORTIF V, which had an almost identical design, but was double-

Table V. Number of patients in the ximelagatran and comparator groups fulfilling criteria for inclusion in the RUCAM analysis

Inclusion criterion[a]	Total	Ximelagatran	LMWH/ warfarin	Placebo
ALT >10 × ULN	113	109	2	2
ALT >3 × ULN and bilirubin >1.5 × ULN	61	53	6	2
ALT >3 × ULN and death at any time	26	22	4	0
First ALT >3 × ULN >6 months after start of therapy	55	40	11	4
First ALT >3 × ULN >1 year after start of therapy	15	12	2	1
Bilirubin >3 × ULN	46	32	10	4
Total number of patients	233	198	25	10

a Each patient can appear in more than 1 group.

ALT = alanine aminotransferase; **LMWH** = low-molecular weight heparin; **RUCAM =** Roussel Uclaf Causality Assessment Method; **ULN** = upper limit of normal.

Table VI. Roussel Uclaf Causality Assessment Method (RUCAM) assessment of the likelihood of hepatic test elevations being related to treatment. Number of patients in each RUCAM category by treatment and pattern of injury

Relationship to treatment[a]	Ximelagatran		Comparator	
	hepatocellular	cholestatic or mixed	hepatocellular	cholestatic or mixed
Excluded	22 (15%)	19 (40%)	10 (67%)	13 (65%)
Unlikely	17 (11%)	12 (25%)	3 (20%)	6 (30%)
Possible	65 (43%)	10 (21%)	2 (13%)	1 (5%)
Probable	46 (31%)	7 (15%)	0 (0%)	0 (0%)
Total	150 (100%)	48 (100%)	15 (100%)	20 (100%)

a Individually assigned RUCAM scores indicate the likelihood of a relationship between study drug and the elevated hepatic test results as follows: ≤0 excluded; 1–2 unlikely; 3–5 possible; 6–8 probable; >8 highly probable. Note that thresholds in the present analysis (i.e. mean RUCAM scores from four hepatologists) were set at ≤0 excluded; >0 to <3 unlikely; ≥3 to <6 possible; ≥6 to ≤8 probable. There was no case in the category 'highly probable' (>8).

blind. However, it cannot be ruled out that raised hepatic enzyme levels were associated with non-specific clinical symptoms in some patients.

The analysis of potential risk factors for ALT levels of >3 × ULN has identified factors other than the administration of ximelagatran that contributed to the raised incidence of ALT elevation. It is not understood why the incidence of ALT levels of >3 × ULN was greater in the two 6-month studies of patients in the post-AMI and VTE-T pools. Female gender was also identified as a potential risk factor, which is in agreement with other analyses of drug-induced hepatotoxicity.[36] The higher frequency of ALT levels of >3 × ULN in patients with low BMI (<25 kg/m^2) is an unexplained finding. There was no indication of an increased risk with concomitant use of statins or aspirin with ximelagatran. None of the differences in incidences related to the positive factors were large enough to identify a group particularly at higher risk; all the odds ratios for these factors were <2, compared with 6.8 for ximelagatran treatment alone. ALT levels of >3 × ULN, studied as a dependent variable in this model, is generally asymptomatic and reversible, therefore, it does not allow prediction of a risk for severe liver injury. As a consequence, there is currently no basis to recommend that any particular group of patients should not be given ximelagatran because of an increased risk of hepatic injury. The usual cautions would apply to those with pre-existing hepatic disease.

A concomitant increase in aminotransferase and bilirubin levels, in the absence of other aetiology, is thought to be predictive of a more severe form of injury.[24,43,44] Elevations of ALT levels of >3 × ULN associated with a concurrent (defined as within 1 month) total bilirubin elevation to levels of >2 × ULN (a modification of 'Hy's rule' for predicting moderate-to-severe acute hepatocellular injury)[24] were observed in 37 patients in the ximelagatran group and 5 patients in the comparator group (presented in table IV). Hy's rule was based on retrospectively reviewed case series of known hepatotoxins (e.g. iproniazid, isoniazid, phenytoin) by Dr Hyman Zimmerman. According to the original observation, drugs causing hepatocellular injury of sufficient severity to cause clinical jaundice (hence, typically associated with bilirubin levels of >3.5–4 × ULN) may be associated with a fatal outcome or need for emergency liver transplant in at least 10% of patients.[45] The FDA has used a modification of the initial observation and called it 'Hy's law' to suggest that it can be used to predict severe hepatic injury based on much more modest elevations in the absence of jaundice in clinical trials.[24] However, 'Hy's law' has never been validated prospectively,[46] the minimal acceptable elevation of subclinical ALT and total bilirubin levels has not been well defined and the rule does not take into account the presence or absence of another aetiology.

It should also be noted that only the total bilirubin level was measured in the clinical trials of ximelagatran, therefore, our analysis would include patients with indirect hyperbilirubinaemia. Unconjugated hyperbilirubinaemia might be associated with Gilbert's syndrome or haemolysis. Elevation of the direct-reacting conjugated bilirubin is more characteristic of hepatocellular injury and this was not specifically determined in our database.

Of the 37 ximelagatran-treated patients with ALT levels of >3 × ULN and total bilirubin levels of >2 ×

Table VII. Outcomes and Roussel Uclaf Causality Assessment Method (RUCAM) assessments of the 22 ximelagatran-treated and 4 comparator-treated patients who had ALT levels of >3 × ULN and who subsequently died

Age (years); gender	Patient group	Time to event (days)		Recovered before death	Cause of death	Type of reaction[a]	RUCAM score[b]
		ALT level >3 × ULN	death				
Ximelagatran							
88; m	AF	101	524	Yes	Sepsis	H	7
75; f	AF	90	312	Yes	Rupture of aorta ascendense	H	7
85; m	AF	93	590	Yes	Death 18 months after recovery of ALT level	H	6.75
78; f	AF	62	446	Yes	MI	M	6.75
80; m	AF	85	145	No	GI haemorrhage[c] (see Appendix, patient 1)	H	4.5
74; m	AF	66	633	Yes	Sudden death	H	4.5
62; m	Post-AMI	61	91	No	Sudden death	M	4.25
77; m	AF	63	82	Yes	GI haemorrhage[c] (see Appendix, patient 2)	M	3.75
64; m	AF	57	502	Yes	Cardiac arrest	H	2.25
75; f	AF	91	118	No	Stroke	H	1
81; m	AF	122	133	No	Cardiomyopathy − sudden death	H	0.75
90; m	Post-AMI	132	133	No	Cardiac failure[c]	C	0.25
74; f	AF	167	221	Yes	Sepsis, pneumonia, lung mass, COPD	H	0
51; m	Post-AMI	27	101	No	Pancreas neoplasm[c]	H	−0.25
65; m	Post-AMI	140	147	No	Renal failure and sepsis	H	−0.25
63; m	AF	155	376	Yes	Aneurysm	M	−0.25
45; m	AF	190	210	Yes	Cardiac failure[c]	M	−0.25
73; m	VTE-T	9	40	No	Reactivation of hepatitis B leading to fulminant hepatitis[c] (see Appendix, patient 3)	H	−0.75
69; m	AF	237	257	No	PE with metastases from gastric cancer[c]	C	−0.75
66; m	AF	285	455	Yes	Cardiac arrest after abdominal pain caused by cholelithiasis[c]	H	−1
54; m	Post-AMI	139	140	No	MI	H	−1.5
76; m	VTE-T	144	144	No	Multiorgan failure following operation of colon carcinoma and liver metastases[c]	H	−2
Comparator (warfarin)							
64; m	AF	63	77	Yes	Sudden death	M	1
79; f	AF	59	582	Yes	Cardiac arrest in a patient with ICM	M	1
76; f	AF	182	528	Yes	MI	H	1
78; m	AF	128	157	No	Pancreas neoplasm[c]	C	0

a Recovered = ALT level of <2 × ULN.

b Individually assessed RUCAM scores indicate the likelihood of a relationship between ximelagatran and the ALT level rise (not the death) as follows: ≤0 excluded, 1–2 unlikely; 3–5 possible; 6–8 probable; >8 highly probable. Note that thresholds in the present analysis (i.e. mean RUCAM scores from four hepatologists) were set at ≤0 excluded; >0 to <3 unlikely; ≥3 to <6 possible; ≥6 to ≤8 probable.

c These 9 ximelagatran-treated and 1 comparator-treated patients are also listed in table IV, as they had bilirubin levels of >2 × ULN.

AF = atrial fibrillation; **ALT** = alanine aminotransferase; **AMI** = acute myocardial infarction; **C** = cholestatic; **COPD** = chronic obstructive pulmonary disease; **GI** = gastrointestinal; **H** = hepatocellular; **ICM** = ischaemic cardiomyopathy; **M** = mixed; **MI** = myocardial infarction; **PE** = pulmonary embolism; **ULN** = upper limit of normal; **VTE-T** = treatment of acute venous thromboembolism.

ULN, 9 died (7 of non-hepatic causes and 1 from fulminant hepatitis due to reactivation of hepatitis B [see Appendix, patient 3], which is a well described complication of his immunosuppressive therapy).[47] A ninth patient sustained an hepatic illness that appeared to be resolving, but was likely to have contributed to his death from a GI haemorrhage (see Appendix, patient 1). Upon review by the panel of hepatologists using the RUCAM method, 9 of these 37 patients with ALT levels of >3 × ULN and bilirubin levels of >2 × ULN were believed to have hepatic aminotransferase level elevation that was 'probably related' to ximelagatran and all recovered. Of the nine patients with concurrent ALT and biliru-

bin level elevation who died sometime after the ALT level elevation, only two (patients 1 and 2 in the Appendix) had a RUCAM score that suggested a 'possible' relationship to ximelagatran. This neither implies nor excludes a relationship between the hepatic injury and the death. A relationship in the other seven was considered to be 'excluded'.

Since the first observation of raised hepatic enzyme levels in patients receiving ximelagatran for >35 days, an algorithm has been in place for frequent testing and reporting of hepatic enzyme results during the clinical trials programme. This algorithm was changed following the single biopsy-documented hepatic necrosis case (see Appendix, patient 1). Although the frequency of ALT levels of >3 × ULN has not been shown to be predictive of the frequency of hepatic failure in the large development programme of ximelagatran, it provides a sensitive screening method to identify potential hepatotoxic effects early and to consider the discontinuation of ximelagatran as a precautionary measure. Consequently, the testing of ALT levels provides a conservative strategy for the prevention of potentially serious hepatotoxicity and is recommended for all patients who can benefit from long-term anticoagulation with ximelagatran. The consistent time profile (1–6 months) for the first occurrence of ALT elevation provides a framework for this risk-minimisation strategy.

A patient risk management and support programme has been developed to educate healthcare professionals and patients about the importance of following the inclusion/exclusion and testing recommendations. ALT level testing has been advocated to prevent the development of severe hepatic events with other useful drugs, such as isoniazid where the likelihood of severe toxicity is in the range of 1 : 1000.[48] The use of monthly ALT level testing for drugs with much less risk, such as for monitoring for the risk of hepatoxicity of statins (estimated at 1 : 100 000), is more controversial. The value of systematic monitoring is limited by the rarity of events, the difficulty of enforcement and the possible evolution of disease between testing intervals.[49] Nevertheless, for a new agent where the toxicity is estimated to be less than isoniazid, but more than that of a statin, a monitoring programme seems reasonable. Its institution prior to approval would differ from that observed for troglitazone, where monitoring was considered unsuccessful but only invoked more than a year after the drug had been on the market.

Despite intensive investigation, the mechanism behind the observed hepatic effect of ximelagatran remains unknown so far. Clinical evidence indicates that the mechanism is not immunoallergic; specifically, no signs of hypersensitivity were observed in the four SPORTIF trials included in this study. In the positive response to reintroduction of ximelagatran observed among 18 patients who were rechallenged, there was no decrease in latency. We also know that the aminotransferase level elevations rarely progressed to symptomatic injury despite the continuation of the drug. As can be seen with many agents causing mainly hepatocellular injury, ALT levels usually returned to normal and this was presumably due to a modulation by host mechanisms that limited further hepatotoxic effects.[50]

Conclusion

Ximelagatran has proven to be effective and well tolerated in the treatment and prevention of thromboembolic complications. In addition, ximelagatran offers fixed oral administration and does not require coagulation monitoring. It provides similar or superior protection versus comparators against the risk of thromboembolic events. Transient elevations in ALT levels have been observed in studies in which ximelagatran has been administered for >35 days. These have mostly been asymptomatic and have improved whether treatment was maintained or not. One patient with subacute biopsy-verified hepatic necrosis was observed in the long-term clinical trials programme. In this patient no other likely aetiology for the hepatic injury was found. The use of ximelagatran in the general population might be associated with higher risks than in the context of a carefully controlled clinical trial protocol. Hence, a widely disseminated patient risk management programme to ensure strict implementation of the ALT testing and management algorithm (figure 1) would be essential to maximise the benefit/risk ratio of the drug. A recent editorial notes the need for diligent post-marketing surveillance; nevertheless, caution regarding the marketing approval of ximelagatran due to concerns about the risk of hepatotoxicity must be

balanced against the risk of discouraging progress in oral anticoagulant therapy, which remains an important and growing therapeutic need.[51]

Although the frequency of ALT levels of >3 × ULN has not been shown to be predictive of the frequency of severe hepatic injury in the extensive development programme of ximelagatran, it provides a sensitive screening mechanism to identify any potential hepatotoxicity early, so that the drug may be discontinued. Further genetic and mechanistic work is being conducted to identify the reason behind the ALT level elevations.

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Appendix

Patient 1

An 80-year-old man with AF began treatment with ximelagatran 36mg twice daily on 11 June 2001. His medical history included hyperlipidaemia, hydronephrosis and urinary retention, fibromyalgia previously treated with prednisone, coronary artery disease treated with bypass grafting and right colon cancer not in evolution. Concomitant medications included metoprolol, digoxin and tamsulosin, which were all taken for several months prior to the start of ximelagatran therapy.

The results of the patient's baseline liver function tests were normal. At the month 2 visit (day 56), his ALT level was mildly elevated at 103 IU/L (2 × ULN), which was less than the threshold that required weekly monitoring. At the scheduled month 3 visit (day 85), his ALT level was 970 IU/L (20 × ULN) and led to weekly liver function testing and discontinuation of ximelagatran.

On day 100, the patient's ALT level was at 1440 IU/L (30 × ULN), ALP level was just above normal and total bilirubin level was nearly 2 × ULN (mainly unconjugated). The search for common causes of hepatic disease was negative (tested by viral serology, immunological markers, and imaging of the liver and abdomen). A liver biopsy on day 108 demonstrated "severe active hepatitis with hepatocyte necrosis, areas of collapse and marked bile ductular proliferation consistent with acute submassive necrosis". Transaminase levels peaked on day 108 and then decreased on day 115. ALP levels peaked at 198 IU/L (1.5 × ULN) on day 115. Total bilirubin level was 8 × ULN on day 114 and remained around this level for a month. On day 112, the patient's synthetic liver function started to deteriorate, as was shown by an increase in the prothrombin time/INR in the absence of anticoagulant therapy and decreased serum albumin levels. The investigator labelled the adverse event as life-threatening hepatic failure and readmitted the patient to hospital on day 113, on which day the patient was jaundiced with no other symptoms and with a normal neurological examination. The patient began treatment with glucocorticoids, vitamin K and ranitidine.

At a visit on day 140, the patient complained of increasing fatigue. Liver enzyme levels continued to improve. The dosage of prednisone was decreased to 15mg daily. Profound fatigue worsened, with no evidence of encephalopathy. However, in the next couple of days the patient's condition quickly deteriorated and he developed ascites, significant lower-extremity oedema and oliguria, and was found dead in his home on day 145.

The main finding at autopsy was a large duodenal ulcer (2.5cm) with erosion into the pancreas. The liver was small, friable and diffusely mottled, which was suggestive of severe diffuse hepatic necrosis. Microscopically, there was extensive liver necrosis with hepatocyte dropout and bile duct proliferation, which was similar to that seen in the previous biopsy. A significant amount of hepatic parenchyma remained. Tissue architecture showed early signs of resolution of the inflammation in comparison with the previous biopsy. The cause of death was an acute GI bleed from a duodenal ulcer, with a coagulopathic state from hepatic injury contributing to death.

Comment: The literature on the use of corticosteroids in the setting of suspected liver failure is difficult to interpret, although most hepatologists do not regard corticosteroids as being overtly beneficial compared with the risks of opportunistic infection developing and the risk of corticosteroid-induced GI bleeding (hence, the use of ranitidine).

This individual was not described as ever having developed encephalopathy and his INR following the discontinuation of ximelagatran peaked at approximately 2.0, but started decreasing after he received fresh frozen plasma. Therefore, he did not fit a strict definition of having acute liver failure.

At the time of his fatal GI bleed, the patient's INR had actually declined further, along with his liver enzyme levels (last values ALT 219 IU/L [4 × ULN], AST 175 IU/L [6 × ULN], INR 1.5). The histology of the liver at the time of necropsy indicated that there was some regeneration and less inflammation than had been seen on the initial liver biopsy weeks earlier.

It is not known if this patient had an underlying ulcer history, but it is reasonable to conclude that corticosteroid therapy may have contributed to bleeding from a duodenal ulcer, which was the fatal event. Whether or not the patient would have eventually recovered from his hepatic necrosis remains unknown, although there are clinical suggestions that he may have recovered since he never fit the true definition of acute fulminant liver failure (given the absence of encephalopathy and coagulopathy). As ximelagatran has a short half-life, its effects on prothrombin time should have been minimal after just a few days. The peak INR of 2.0 is likely to reflect the underlying hepatic injury, but in cases of irreversible liver failure, the prothrombin time and INR continue to rise despite efforts at reversing the coagulopathy.

Patient 2

A 77-year-old man with AF began treatment with ximelagatran 36mg twice daily on 13 August 2001. His medical history included a cholecystectomy 2 years earlier, duodenal ulcer, a bleeding bladder (in 2000), psychosis, gout, alcohol abuse, osteoarthritis, pulmonary insufficiency, abdominal aortic aneurysm repair (April 2001), arterial hypertension, cardiomyopathy and coronary disease. Concomitant medications included carvedilol and ramipril.

His baseline ALT level was normal, but at day 63 was 216 IU/L (>4.5 × ULN). Bilirubin level was normal. Requests to have him return for repeat laboratory tests 3 and 7 days later went unheeded by the patient. He took his last dose of ximelagatran on day 80. However on day 81 he developed abdominal pain and haematochezia and was admitted for massive upper GI bleeding and severe hypotension (76/45mm Hg) that was determined to be from an anastomotic ulcer from his previous Billroth II anastomosis for ulcer disease.

On admission, his haemoglobin level was 7 g/dL, ALT 569 IU/L (>11 × ULN), AST 629 IU/L (>15 × ULN), bilirubin 1.4 × ULN and he had an elevated INR of 3.4. The patient received a massive transfusion of blood products given in a resuscitation effort, including 19 units of packed red cells, 30 units of cryoprecipitate and 15 units of fresh frozen plasma and vitamin K. Within 24 hours of this (day 82) his coagulopathy had resolved temporarily, ALT level had decreased to 97 IU/L (1.9 × ULN), but total bilirubin level was 9.4 × ULN (50% unconjugated).

The patient developed respiratory failure and pulmonary oedema that did not respond well to furosemide. Vasopressors and fluids were given to sustain blood pressure and diltiazem to reduce a rapid heart rate. Synchronised cardioversion failed four times to restore sinus rhythm and shock persisted despite resuscitation efforts with fluids, red blood cells, fresh frozen plasma and platelets. Profound coagulopathy occurred, the abdomen became rigid, gastric suction yielded blood and support was withdrawn. The patient was judged to have died on day 82 as a result of massive haemorrhage. No autopsy was conducted.

Comment: The massive transfusion of blood products can explain the indirect hyperbilirubinaemia, which is related to red cell breakdown with massive overproduction of bilirubin. Evidence in support of haemolysis includes a nearly absent haptoglobin level, elevated lactate dehydrogenase level and the exclusion of disseminated intravascular coagulation. This patient is listed as a 'Hy's rule' patient because of this elevation in bilirubin level, which occurred within 30 days of the ALT level rising. It is possible that the bleeding was precipitated by the use of ximelagatran in a patient with a silent ulcer and prior ulcer history, but it is not at all clear whether the patient had irreversible hepatic injury from the drug.

The case has been adjudicated as 'possibly related' to the study drug because we do not have enough information to exclude the possibility that the drug

was involved in the initial rise in ALT level. No biopsy or autopsy was ever performed. However, the elevated AST >ALT levels on admission, in the setting of marked hypotension from bleeding, suggests shock liver was present (possible liver ischaemia), although the initial elevation in ALT levels may have been drug-related. The patient died of multisystem organ failure following the massive haemorrhage. The validity of invoking Hy's rule in this case appears tenuous given the indirect hyperbilirubinaemia that most likely resulted from massive transfusions. As a result, its predictive value for signalling acute liver failure is also highly confounded.

Patient 3

A 73-year-old man with VTE began treatment with ximelagatran 36mg twice daily on 10 January 2002. He had a history of lupus (anti-nuclear autoantibodies 1 **:** 5120) and had underlying chronic hepatitis B infection (hepatitis B surface antigen positive and hepatitis B e-antigen positive) with elevated ALT levels of 93 IU/L (1.94 × ULN) and AST levels of 123 IU/L (2.24 × ULN) at baseline, prior to initiating ximelagatran therapy. He also had a history of gastric ulcer and diabetes mellitus. This patient was receiving immunosuppressive therapy (azathioprine and prednisone) for his underlying lupus and was not receiving treatment or prophylaxis for his hepatitis B.

On day 9 the patient had mild transaminase level elevation. On day 18 he was hospitalised based on positive serology for hepatitis B. His ALT level was 327 IU/L (7.7 × ULN) and his AST level was 481 IU/L (8.7 × ULN.) On day 24, ximelagatran was discontinued and the patient's condition was good with no sign of liver failure. However, the patient appeared to develop progressive hepatitis by day 26: ALT 518 IU/L (14.8 × ULN), AST 593 IU/L (16.9 × ULN) and total bilirubin 40 mg/L (3.6 × ULN), rising to 268 mg/L (24.4 × ULN). The patient's condition subsequently deteriorated and he developed ascites, which was followed by signs of encephalopathy. He had multiple gastric ulcers detected on endoscopy for abdominal pain and melena. Rapid deterioration led to coma, support was withdrawn and he died 2 days later. No autopsy was performed.

Comment: Under the current proposed management algorithm, this patient should not have received ximelagatran because of his hepatic disease. The development of progressive hepatitis at day 26 is likely to be the result of acute reactivation of underlying hepatitis B infection in a patient receiving corticosteroid/azathioprine immunosuppression. The patient did have evidence of active viral replication with hepatitis B e-antigen being positive. This was not acute hepatitis B, as the hepatitis B core IgM antibody was negative and the total core was positive. There is no information about whether this could have been a superinfection with Delta virus. There is no reason to suspect ximelagatran in the presence of immunosuppressive therapy.

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Correspondence and offprints: Dr *William M. Lee*, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-9151, USA.
E-mail: william.lee@utsouthwestern.edu