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Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH)

Application of this Data Organization Approach to Phase III Clinical Trials of Rivaroxaban after Total Hip or Knee Replacement Surgery

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Abstract

Background: The most specific indicator of a drug-induced liver injury signal in a clinical trial database is believed to be the occurrence of subjects experiencing drug-associated elevations in both serum ALT and serum total bilirubin (TB) without a significant elevation in serum alkaline phosphatase (ALP). eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) is a recently described tool that organizes liver laboratory data by graphically displaying peak serum ALT and TB levels for each subject, and can also provide direct links to the pertinent clinical and laboratory data for each subject.

Objective: To illustrate the usefulness of the eDISH approach in the presentation of liver safety data by using phase III clinical trial data for rivaroxaban.

Methods: Four randomized, active-controlled studies were conducted worldwide in subjects undergoing elective hip or knee replacement surgery to compare the efficacy and safety of the anticoagulant rivaroxaban, an oral, direct Factor Xa inhibitor, with the low-molecular-weight heparin, enoxaparin. Liver laboratory assessments, including ALT, AST, TB and ALP, were performed frequently during the studies. Data were incorporated into eDISH and linked data for selected subjects were analysed.

Results: In the pooled analysis of the four studies, a total of 12 262 subjects (6131 rivaroxaban, 6131 enoxaparin) received at least one dose of study

drug and had at least one central and/or local laboratory assessment during the study. A total of 143 (2.33%) rivaroxaban subjects and 223 (3.64%) enoxaparin subjects experienced a peak ALT >3×upper limit of normal (ULN) but did not experience an elevation of TB >2×ULN; these subjects are displayed in the right lower quadrant of the eDISH plot, termed the 'Temple's Corollary quadrant'. There were ten rivaroxaban and ten enoxaparin subjects with a peak ALT >3×ULN and a peak TB >2×ULN; these subjects were displayed in the right upper quadrant of the eDISH plot, termed the 'Hy's Law quadrant'. eDISH allowed efficient examination of the relevant data for each of these subjects.

Conclusions: The eDISH approach is an efficient and effective way to organize and examine large liver safety databases for randomized controlled clinical trials. It greatly facilitates a systematic and transparent examination of the relevant liver safety laboratory data. We believe eDISH should become a standard approach for assessing and studying liver safety issues in clinical trials.

Background

Drug-induced liver injury is the most frequent adverse drug reaction leading to termination of clinical development programmes prior to market authorization or leading to withdrawal of drugs after approval.[1] A thorough evaluation of liver safety prior to market authorization is therefore necessary and expected by regulatory authorities. The US FDA worked with leaders in academia and industry to produce a guidance document that outlines an approach to assessing liver safety databases from clinical trials.[2] This guidance document points out that serum ALT is a sensitive but not specific biomarker for drugs that have potential to cause serious liver injury. This is because there are drugs that can produce ALT elevations, even high elevations in some patients, but that have either no risk or a very low risk of causing clinically important liver injury (e.g. heparins, HMG-CoA reductase inhibitors ['statins'], tacrine). Consequently, examination of only ALT levels is not a specific way to assess the potential for a new drug to cause clinically important liver injury.[3] The guidance document stresses that the most specific biomarker of potentially serious liver injury is the concomitant elevation of serum ALT and serum total bilirubin (TB), signalling dysfunction of the liver.

An efficient way to examine and summarize ALT and bilirubin levels in a clinical trial is through a tool named eDISH (evaluation of Drug-Induced Serious Hepatotoxicity). The eDISH[4] tool was conceptualized by Dr John Senior at the FDA to allow medical reviewers to display the peak serum ALT and TB values for every subject in a clinical trial. eDISH allows each point in the display to be directly linked to all liver chemistry values obtained for that subject, as well as other pertinent clinical data. Medical reviewers at the FDA have begun to use eDISH when evaluating a liver safety database from phase III clinical trials (Senior J, personal communication). To our knowledge, eDISH has not been widely adopted within the pharmaceutical industry.

Rivaroxaban is an oral, direct Factor Xa inhibitor that was evaluated in four phase III clinical trials for prophylaxis of deep vein thrombosis and pulmonary embolism in subjects undergoing elective total hip or knee replacement surgery.[5-8] We utilized the eDISH approach to organize and present the liver safety data at the March 2009 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. We summarize this

presentation here to illustrate the utility of the eDISH approach.

Methodology

Study Design

Four randomized, double-blind, double-dummy, active-controlled, phase III studies (RECORD [REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE] studies) were conducted worldwide. Patients were randomized to receive oral rivaroxaban 10 mg once daily administered 6–8 hours after wound closure, or after adequate haemostasis had been achieved, or subcutaneous enoxaparin 40 mg once daily starting the evening before surgery (RECORD1–3), or 30 mg twice daily commencing 12–24 hours after wound closure (RECORD4). In both RECORD1 and 2, patients undergoing elective total hip replacement were given rivaroxaban for 35 ± 4 days. Enoxaparin was given for 35 ± 4 days in RECORD1 or 10–14 days followed by placebo in RECORD2. In RECORD3 and 4, patients undergoing elective total knee replacement received prophylaxis for 12 ± 2 days. Additional details on study design and results from the RECORD studies are reported elsewhere.[5-8]

Liver Safety Assessments

Protocol-specified liver-related laboratory assessments by a central laboratory were performed in the RECORD studies and included ALT, AST, TB and alkaline phosphatase (ALP). These laboratory assessments were performed on days 0, 1, 6 (RECORD2 only), 13, 36 and 65 in RECORD1 and 2, and on days 0, 1, 6, 13 and 42 in RECORD3 and 4 (day of surgery was day 1). All laboratory tests on scheduled visits were performed in a single central laboratory. Unscheduled laboratory test results obtained from a local laboratory, when available, were also collected and analysed. An assessment of adverse events also occurred on the same days as laboratory assessments in each of the RECORD studies.

eDISH Assessment

On an eDISH plot the peak serum ALT is shown along the x-axis, and the peak serum bilirubin is shown along the y-axis as multiples of (*x*-fold) the upper limits of normal (ULN) on log scales. The use of a log scale facilitates the presentation of ALT and TB data in subjects with a wide range of values. Each point in the eDISH plot represents the values for a single individual. Subjects who have received at least one dose of study drug and have had at least one ALT and one TB assessment are displayed. Subjects with substantial elevations tend to be of greater clinical interest. A second feature of the eDISH tool is the potential to link each subject's point in the plot to additional liver laboratory data and/or clinical data collected during the course of the study. This data-linking feature requires some additional programmatic steps that were not available at the time of our analysis. Therefore, the time course of serum liver chemistries was manually extracted from the study databases.

Four quadrants are defined by a line corresponding to three times the ULN for serum ALT and a line corresponding to twice the ULN for TB. The right upper quadrant includes all subjects with serum ALT greater than three times the ULN, but who also had elevation of TB greater than twice the ULN. This combination of laboratory abnormalities has been proposed as the most specific indicator for a drug's potential for causing serious liver injury[2] and represents an adaptation of the original clinical observation made many years ago by the US hepatologist Dr Hyman Zimmerman.[9,10] Drawing on his extensive experience with a number of drugs in circumstances in which he and his colleagues collected cases reported to the FDA or the Armed Forces Institute of Pathology, Zimmerman made the following observation: drug-induced hepatocellular injury (marked elevation of serum transaminases with no or minimal elevations in serum ALP) accompanied by clinical jaundice is associated with a mortality of at least 10% (range 5–50%).[2,10] Initially termed 'Hy's Law' by others, over time a modification developed replacing clinical jaundice with TB greater than twice the

ULN (below the jaundice threshold of the original observation) in an attempt to be predictive of more severe acute liver failure while using the objectivity of laboratory criteria.[2] It is for these reasons that this upper right quadrant is labelled 'Hy's Law'.

The right lower quadrant is labelled 'Temple's Corollary', reflecting an observation first made by Dr Robert Temple of the FDA that an imbalance in this quadrant between those subjects treated with study drug and those treated with a non-hepatotoxic comparator (or placebo) has been reliably present with drugs capable of causing serious liver injury, even when examination of the Hy's Law quadrant was unrevealing.[2] This is because ALT is a much more sensitive indicator of hepatocellular injury than bilirubin and increases are expected to occur before or without accompanying rises in TB.[2] An imbalance between treatment and comparator in the Temple's Corollary quadrant does not in itself constitute a clear liver safety signal. For example, heparin and its derivatives cause frequent ALT elevations exceeding three times the ULN,[11-13] but have rarely, if ever, caused serious liver injury.

The left upper quadrant is labelled the 'Cholestasis' quadrant and includes subjects with a TB greater than twice the ULN along with an ALT less than three times the ULN. An overrepresentation of points on study drug relative to control would be expected in this quadrant for drugs that are associated with cholestatic liver injury. The left lower quadrant represents subjects never showing an ALT greater than three times the ULN or a TB greater than twice the ULN.

It is the intent of the developers of the eDISH analytical system (Drs Senior and Guo) to make this software publically available in the near future if possible (Senior J, personal communication).

Hy's Law Cases

The FDA guidance recognizes that not all subjects experiencing serum ALT exceeding three times the ULN and serum TB exceeding twice the ULN represent a serious liver safety signal.[2] The document therefore defined the 'Hy's Law case' as a subject appearing in the Hy's Law quadrant on the eDISH plot, but who also fulfills three additional criteria. First, the subject must have a hepatocellular injury defined as "without initial findings of cholestasis (i.e. elevated serum ALP)".[2] Second, there should not be a more likely explanation for the liver injury observed, such as passing a gall stone or contracting viral hepatitis. Finally, there should be a higher incidence of ALT elevations greater than three times the ULN in the drug-treated subjects relative to subjects treated with the comparator in the clinical trials, assuming that the comparator does not itself cause ALT elevations. The comparator in the RECORD clinical trials was enoxaparin, which is well known to cause ALT elevations.[13] For this reason, the third criterion was not employed in our analysis and hence only 'potential' Hy's Law cases could be identified among subjects receiving rivaroxaban therapy.

Results

In the four pooled studies, a total of 12 383 subjects were randomized and received at least one dose of study drug (6183 rivaroxaban, 6200 enoxaparin). Of these subjects, 12 262 (6131 rivaroxaban, 6131 enoxaparin) had at least one central and/or local laboratory assessment for ALT and TB during the study. Their mean age (± SD) was 64.1 ± 11.2 years, 60% were female, 79% were Caucasian and 10% were Asian. There were no imbalances between the treatment groups in terms of demographic characteristics, including age, sex and body mass index.[5-8]

Figure 1 shows the eDISH plot for the pooled RECORD studies. In the right lower quadrant (Temple's Corollary quadrant), there were 143 (2.33%) rivaroxaban subjects and 223 (3.64%) enoxaparin subjects with a peak ALT greater than three times the ULN and a peak TB less than twice the ULN. In the right upper quadrant (Hy's Law quadrant), there were a total of ten rivaroxaban subjects and ten enoxaparin subjects observed to have a peak ALT greater than three times the ULN and a peak TB greater than twice the ULN determined concurrently (same calendar day) or non-concurrently (different

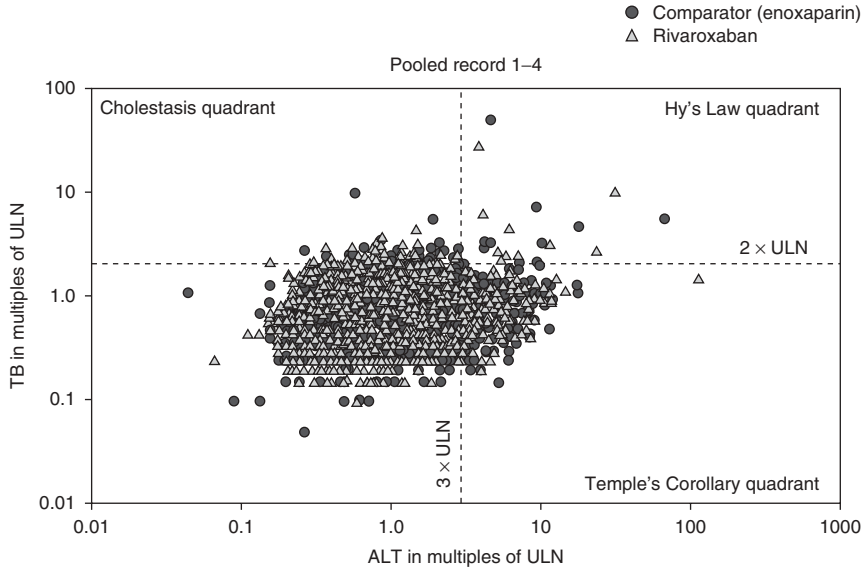

Fig. 1. Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot from the pooled RECORD (REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE) studies. Each point in the figure represents a unique subject's peak serum ALT and peak serum total bilirubin (TB) values. Peak serum ALT is shown along the x-axis and peak TB is shown along the y-axis as *x*-fold upper limits of normal (ULN) on a log scale.

calendar days) by either central or local laboratory testing.

Of the 20 subjects in the Hy's Law quadrant, 17 met the criteria for elevation of ALT greater than three times the ULN and elevation of TB greater than twice the ULN on the same calendar day. Three subjects (two rivaroxaban, one enoxaparin) never met both criteria of elevation of peak ALT and elevation of peak TB simultaneously. In two (one rivaroxaban, one enoxaparin) of these three subjects, the apparent elevation in TB was determined to be a data entry error and these two subjects were therefore excluded from further analysis. The remaining (third) enoxaparin-treated subject had a TB value exceeding twice the ULN (2.5 mg/dL) on day 2 with a peak ALT greater than five times the ULN (319 U/L) on day 11, at which point the TB was normal. This pattern is not consistent with hepatocellular injury producing liver dysfunction, therefore this patient also was not evaluated further. There were no subjects with ALT greater than three times the ULN who first experienced TB exceeding twice the ULN after ALT had returned to less than three times the ULN, a pattern that could be consistent with liver dysfunction as a result of a hepatocellular injury.

Identification of Potential Hy's Law Cases

Table I applies the two applicable criteria for a Hy's Law case (see Methods section) to the nine rivaroxaban subjects and eight enoxaparin subjects in the Hy's Law quadrant with peak elevations of ALT greater than three times the ULN, and TB greater than twice the ULN occurring on the same day. Three subjects who never met the criteria of simultaneous elevations of peak ALT and peak TB have been described in the Results section. The rivaroxaban-treated subject with the highest recorded serum ALT values (30 times the ULN) received study drug for 36 days and experienced a pronounced spike in liver enzymes that resolved off therapy (figure 2). Although it initially seemed that this event was probably treatment related, serological evaluation clearly showed that this subject experienced an acute hepatitis C infection. Hepatitis C virus was not

Table I. Summary findings of subjects meeting criteria for ALT greater than three times the upper limit of normal (ULN) and total bilirubin (TB) greater than twice the upper limit of normal concurrently (on the same calendar day)[a]

Finding	Rivaroxaban (n = 9)	Enoxaparin (n = 8)
Elevated alkaline phosphatase (>2 × ULN)	4	2
Elevations occurred before study drug	2	0
Clear alternate explanation	1 (acute hepatitis C)	3 ('shock liver', Gilbert's syndrome, common bile duct blockage[b])
No clear alternate explanation	2[c]	3[d]

a Three subjects who never met the criteria for ALT greater than three times the ULN and TB greater than twice the ULN on the same calendar day are not included in this table.

b Both Gilbert's syndrome and common bile duct blockage are conditions that can cause elevations in serum TB in the absence of liver injury.

c One case from RECORD 1 and one case from RECORD 2. In one case, direct bilirubin was <50% of TB.

d One case each from the RECORD 1, 2 and 3 trials. In one case, direct bilirubin was <50% of TB.

RECORD = REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE.

detectable by polymerase chain reaction or antibody tests in this subject's stored pretreatment serum sample, but both antibody and polymerase chain reaction tests became positive during the liver injury event. The subject completely recovered.

The enoxaparin-treated subject with the highest recorded serum ALT (67 times the ULN) values also had liver enzyme elevations on treatment that resolved after study drug discontinuation, consistent with a treatment effect. However, this subject had documented congestive heart failure and a documented episode of hypotension, and thus the most likely cause for the liver injury was ischaemic hepatitis or 'shock liver' (figure 3). The five potential Hy's Law cases with no clear alternate explanation (table I) are discussed below.

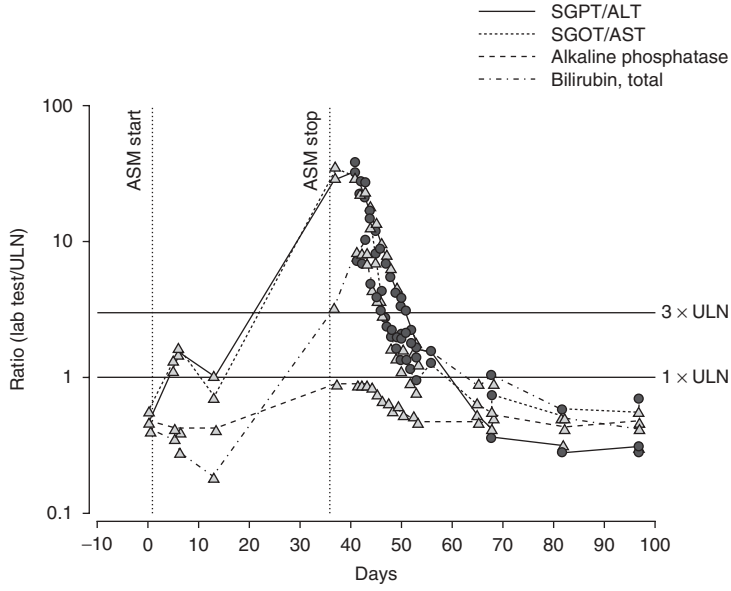

Fig. 2. Time course of liver chemistries in a 49-year-old Indonesian male with documented acute hepatitis C infection. The x-axis represents time in days from surgery and the y-axis represents absolute laboratory values divided by the corresponding upper limit of normal (ULN; i.e. × ULN). This subject was randomized to rivaroxaban therapy. Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) can allow for instant visualization of this display for each subject by clicking on a specific subject point in the eDISH plot (figure 1). **ASM** = active study medication; **SGOT** = serum glutamic oxaloacetic transaminase; **SGPT** = serum glutamic pyruvic transaminase; **circles** represent local laboratory assessments; **triangles** represent assessments performed in the central laboratory.

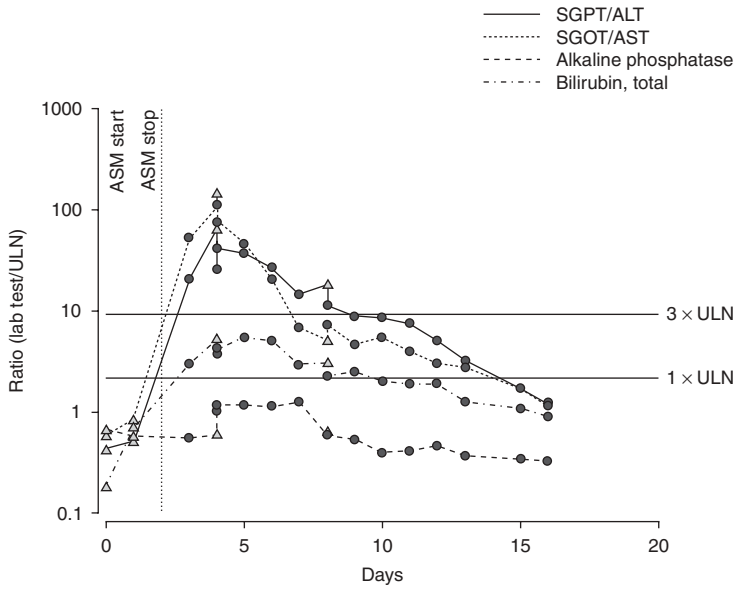

Fig. 3. Time course of liver chemistries in a 40-year-old Indian female with probable ischaemic hepatitis. The x-axis represents time in days from surgery and the y-axis represents absolute laboratory values divided by the corresponding upper limit of normal (ULN; i.e. × ULN). This subject was randomized to enoxaparin therapy. **ASM** = active study medication; **SGOT** = serum glutamic oxaloacetic transaminase; **SGPT** = serum glutamic pyruvic transaminase; **circles** represent local laboratory assessments; **triangles** represent assessments performed in the central laboratory.

One subject treated with rivaroxaban had unremarkable liver chemistries during his 10-day treatment course. About 6 weeks later, when he next had blood tests, his ALT was greater than 20 times the ULN (1062 U/L) and TB was three times the ULN (3 mg/dL). The subject was apparently asymptomatic and follow-up ALT obtained 2 weeks later was entirely normal (not shown). The other subject receiving rivaroxaban had an ALT greater than three times the ULN and TB greater than twice the ULN concurrently on one occasion, but the time course of the liver chemistries showed that the peak of the TB elevations occurred 1 week prior to the ALT peak, a pattern not typical for hepatocellular jaundice. Of the remaining three subjects receiving enoxaparin with no clear alternate explanation, one was a subject with an asymptomatic, peak ALT elevation greater than four times the ULN (190 U/L) at 14 days after the start of study medication, with a peak TB greater than three times the ULN (3.5 mg/dL) that also occurred on the same day. The study drug was stopped and liver chemistries subsequently resolved (figure 4). The second subject also experienced asymptomatic elevations in ALT greater than six times the ULN (319 U/L) on day 3, with a corresponding peak TB just over twice the ULN (2.1 mg/dL). Liver chemistries began to improve despite continuation of therapy with enoxaparin, and completely resolved after discontinuation of therapy (figure not shown). In the last of the three enoxaparin cases, asymptomatic liver chemistry elevations were observed with a peak ALT greater than three times the ULN (146 U/L) on day 7 and a peak TB exceeding three times the ULN (3.8 mg/dL) on day 1 (TB was 2.7 mg/dL on day 7). The laboratory values were near normal on day 13, the last day of study drug administration (figure not shown).

Discussion

The database for the RECORD clinical trials contained subjects with abnormalities in liver chemistries, including subjects with elevations in

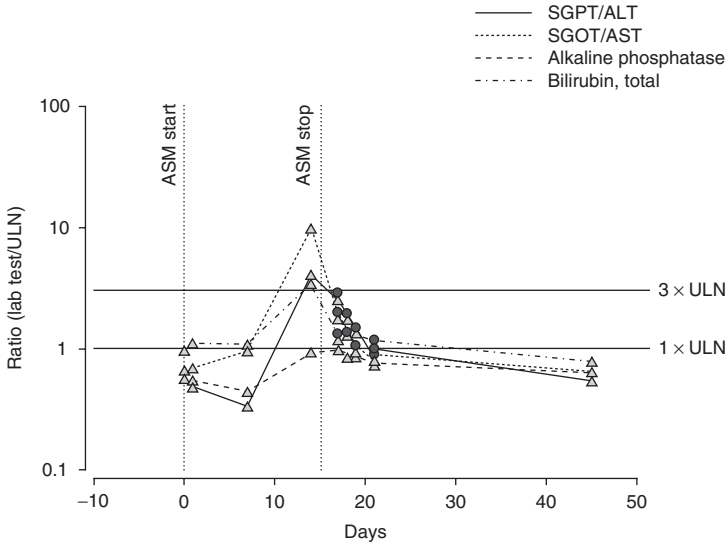

Fig. 4. Time course of liver chemistries in a 74-year-old Polish male with an unexplained ALT >3× upper limit of normal (ULN) and a total serum bilirubin >2× ULN. The x-axis represents time in days from surgery and the y-axis represents absolute laboratory values divided by the corresponding ULN (i.e. × ULN). This subject was randomized to enoxaparin treatment. **ASM** = active study medication; **SGOT** = serum glutamic oxaloacetic transaminase; **SGPT** = serum glutamic pyruvic transaminase; **circles** represent local laboratory assessments; **triangles** represent assessments performed in the central laboratory.

both serum ALT and TB, as would be expected in the postoperative setting. The eDISH plot allowed simultaneous display of the peak ALT and TB from all subjects enrolled in the clinical trials. The division into four quadrants allowed immediate comparison of the effects of rivaroxaban versus enoxaparin in terms of serum elevations in ALT greater than three times the ULN or TB levels exceeding twice the ULN. Importantly, Hy's Law quadrant cases allowed immediate comparison between treatments in the number of subjects, with the combined abnormalities thought to be the most specific indicator of a drug's potential to cause progressive and clinically important liver injury. In this case, the incidence was balanced; ten subjects treated with rivaroxaban and ten subjects treated with enoxaparin.

By linking the points on the eDISH plot to the subjects' serial (graphed) liver chemistries and pertinent clinical data, it was possible to examine each subject in the Hy's Law quadrant to determine whether they met the qualifications for a Hy's Law case as set forth in the FDA guidance.[2] Two subjects were found to have data entry mistakes that erroneously placed them in the Hy's Law range, and in two rivaroxaban-treated subjects, the qualifying laboratory results occurred before they actually received the drug. One subject had a pattern of liver injury where peak TB preceded peak ALT, which is not consistent with the typical pattern for drug-induced liver injury. Six additional potential Hy's Law cases could be excluded because they experienced a largely cholestatic liver injury, manifested by elevations in serum ALP exceeding twice the ULN. This exclusion criterion is based on the observation that TB elevations occur early during a cholestatic liver injury and do not necessarily signify liver dysfunction. This is not to say that cholestatic liver injuries are always benign but they are much less frequently associated with fulminant acute liver failure.[14] Because the subject becomes jaundiced early in the course of a cholestatic injury, it is more likely that the toxicity will be recognized in time to safely stop the implicated treatment. Routine liver chemistry monitoring is rarely recommended for drugs that typically cause cholestatic injuries.

It is more likely that etiologies other than drug-induced liver injury were involved in six

cases in the Hy's Law quadrant. This left two rivaroxaban- and three enoxaparin-treated subjects who fulfilled the criteria for a potential Hy's Law case. However, one of the two rivaroxaban-treated subjects experienced their peak TB values before the serum ALT rose to greater than three times the ULN, and this is not consistent with TB rise secondary to hepatocellular injury. In the remaining rivaroxaban-treated patient in the Hy's Law quadrant, the laboratory pattern is consistent with liver dysfunction secondary to a hepatocellular injury. The subject had normal values during his 10-day treatment course but about 6 weeks later his ALT was 1062 U/L and TB was 3 mg/dL. The subject was apparently asymptomatic and follow-up ALT obtained 2 weeks later was entirely normal. There was an incomplete evaluation of alternate etiologies in this case.

There were three enoxaparin-treated subjects who met the criteria for a Hy's Law case and, since enoxaparin causes ALT elevations greater than three times the ULN,[13] these cases would fit the full criteria for a Hy's Law case as defined in the FDA guidance.[2] In other words, if enoxaparin was the new drug being tested and rivaroxaban was the comparator, the existence of these three Hy's Law cases would currently be viewed as a serious liver safety signal. However, we know that low-molecular-weight heparins such as enoxaparin rarely, if ever, cause clinically important liver injury.[13] It is quite possible that enoxaparin caused the ALT elevations observed in these three enoxaparin-treated subjects and that some other event (blood transfusion or blood resorption at the surgery site) caused the rise in TB. It is also possible that other medications received by these subjects (e.g. anaesthesia, antibiotics, NSAIDs) may have contributed to elevations in ALT and possibly TB.

It should also be noted that the rivaroxaban-treated subject with the highest serum ALT value (figure 2) was initially presumed to have experienced a drug-induced liver injury. However, serological evaluation revealed that this subject unequivocally experienced an acute hepatitis C infection. Hepatitis C virus was not detectable by both antibody and polymerase chain reaction tests in this subject's stored serum obtained before treatment, but both tests became positive during the liver injury event. Without the saved baseline serum sample, it would not have been possible to confidently make the diagnosis of acute hepatitis C. This magnitude of ALT elevations in the absence of a plausible alternative (i.e. acute hepatitis C) would be considered as a Hy's Law case.

It should be further noted that the absence of Hy's Law cases in clinical trials does not necessarily mean that the study drug will have complete liver safety post-approval. Clinical trials often have exclusion criteria, such as certain concomitant illnesses or medications that may increase patient susceptibility to liver injury, or ability to withstand liver injury. In addition, patients may be more closely monitored in clinical trials and discontinue treatment before the liver injury could progress to qualify as a Hy's Law case.

As a final point, it is likely that there exist more reliable biomarkers of drug-induced liver injury than the Hy's Law case,[3] and at least one industry consortium has placed a high priority on finding such biomarkers.[15] This effort will require analysis of large numbers of serum samples, and perhaps other biospecimens, obtained serially from patients treated with drugs capable of causing serious liver injury, as well as from patients treated with drugs that do not cause serious liver injury but may nonetheless produce alterations in traditional liver chemistries. eDISH would appear to be an ideal, standardized way for participating companies to store relevant liver safety data from clinical trials, especially by linking eDISH directly to biospecimen repository databases.

Conclusions

The eDISH approach is a highly efficient and effective way to examine and summarize ALT and TB levels from randomized controlled clinical trials. It allows a systematic and transparent examination of the relevant liver safety data and we believe it should become a standard approach for assessing and investigating liver safety issues in clinical trials.

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