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ALT as a Biomarker for Drug-Induced Liver Injury

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Introduction

Because there is presently no definitive biomarker for drug-induced liver injury (dili), causality assessment for dili is currently an inexact science

Reliance for considering possibly developing dili continues to depend on identifying abnormal serum enzymes, predominantly alanine aminotransferase (ALT), but also aspartate aminotransferase (AST) and, alkaline phosphatase (ALKP)

However, the use of the ALT as a signal for potentially developing hepatocellular dili has shortcomings and associated uncertainties



Shortcomings Related to Use of the ALT as a Dili Biomarker

A raised ALT value is a non-specific marker of liver injury, so that dili can be considered only after excluding all other causes of liver injury

There is no consensus on what level of ALT increase during treatment should signal possible impending dili - 3X, 5X, 8x, other?

Whatever the agreed-upon ALT value, it's fold increase is calculated against a baseline value, generally the "upper limit of normal" (ULN), but there is dispute regarding what that level is

With the advent currently of direct acting anti-virals against hepatitis C, drugs are now being given to persons with abnormal ALT values at the outset, the very marker used to signal dili



DILI Assessment Differs Between Clinical Trials and Clinical Practice

The issue is also complicated by the fact that elements available for considering DILI differ according to whether the liver injury occurred in pre-marketing clinical trials or in clinical practice

In clinical trials, pretrial and baseline ALT testing and on-treatment ALT monitoring is required, thus providing all components needed for comparative analysis

In clinical practice, possible DILI is first recognized when jaundice or symptoms develop within 6 to 9 months of starting treatment, but there is generally no baseline or pre-illness ALT levels with which to compare the identified abnormal ALT level



Impact of ALT as a Nonspecific Diagnostic Marker of Dili

Because an abnormal ALT value is only a non-specific indicator of liver injury, linking it to possible impending dili requires that all other causes for hepatocellular injury first be excluded

Clearly, this circuitous way of making a diagnosis is far from ideal, underscoring the need for more specific biomarkers

The result of this protracted method of diagnosing dili is that it adds considerable cost to making the diagnosis and also may result in the unnecessary withholding of an important drug while confirming the diagnosis, which could have adverse effects



What Level of Identified Abnormal ALT Should Signal Possible Impending Dili?

Until recently, most clinical trials have required study participants to have normal ALT levels at study outset in order to minimize confusion should abnormalities occur during treatment

Most trials have then required bi-weekly or monthly ALT monitoring to screen for possible developing dili, affording early identification of an abnormal ALT level

The question is what should the abnormal ALT level be that triggers concern of possible developing dili?



ALT Fold Increase as a Signal for Impending Dili?

In general, ALT levels in the normal range remain normal and vary little over time in persons without liver disease

It can be argued, therefore, that as little as a 2-fold increase in the ALT level in monitored persons with prior normal values can raise concern for impending dili in the appropriate setting

However, this level of ALT increase is rarely accepted as a reason to withhold a drug, unless accompanied by symptoms or jaundice, although it should trigger repeat ALT testing

Thus, higher levels as signals for possible developing dili have been suggested, but each are simply arbitrary choices



Suggested ALT Fold Increases as a Signal for Impending DILI?

Levels suggested as more suitable signals include a 3-fold increase*, a 5-fold increase**, and even an 8- to 10-fold increase***

The reason given for preferring the 5-fold to the 3-fold increase is to limit the inclusion of persons with pre-existing liver disease, especially NAFLD

This is probably not an issue in clinical trials since subjects with abnormal ALT levels are generally excluded

Accordingly, a 3-fold ALT increase during the course of treatment seems the most practical and appropriate signal

*FDA Guidance, Regev A, et al. Drug Saf 2014; **Aithal GP, et al. Clin Pharmacol Ther 2011; ***Some Clinical Trials



Baseline Comparator ALT Level?

The raised ALT level signaling possible developing liver disease is graded as a fold increase relative to a pre-treatment baseline ALT level

Traditionally, the baseline comparator ALT level used is what is regarded as its upper limit of normal (ULN)

The ULN is determined for each laboratory by screening a large local population believed to be "healthy" and then selecting as a reference number the mean value ± 2 standard deviations (95th percentile)

Unfortunately the screened local population is not always healthy, some having unrecognized NASH causing raised ALT levels, thus increasing the mean level of the ALT



Baseline Comparator ALT Level?

If several research laboratories participate in a clinical trial, it is then likely that there will be differing levels identified as the ULN of ALT

This will have an obvious impact in defining the fold increase level used to signal impending dili

To avoid this problem, the baseline comparator used to establish a given ALT fold increase would have to be the ULN value established by each laboratory separately and not a hypothetical group normal value

A preferable alternative is to use each individual's own baseline ALT value as the comparator



Dili Monitoring Guidelines for Persons With Pre-Existing Abnormal ALT Levels

The advent of multiple direct acting anti- viral drugs (DAAs) has opened the way to treat patients with chronic hepatitis C, most of whom have increased ALT levels prior to treatment

Other common chronic liver diseases currently or likely in the future to be involved in treatment trials are chronic hepatitis B and the fatty liver conditions, NASH and NAFLD

For these individuals with already raised ALT levels at outset, the use of the ALT as a signal for possible dili is problematic

Moreover, the FDA Guidelines for Industry have not defined rules for persons who enter trials with abnormal enzymes



Effectiveness of DAAs in Treatment of Chronic Hepatitis C

Treatment with the DAAs has been remarkably successful, over 90% of treated patients achieving undetectable virus levels and normalized ALT values within a week or two

However, treatment generally continues for a full 12 weeks during which time liver damage might yet develop

This raises the question of what the comparator should be if an elevated ALT develops thereafter - the original baseline abnormal ALT level, or the new on-treatment normal ALT level?



Failure of Response to DAA Treatment

For the few treated patients who fail to respond to treatment, any unusual future ALT increase should be measured against the patient's own baseline abnormal ALT level, not some hypothetical group normal

The following approach is suggested: if the abnormal baseline ALT value does not exceed 100 U/L, a 3-fold ALT increase over the baseline would represent an increase of concern; if the baseline ALT is abnormal but exceeded 100 U/L, a 2-fold ALT increase over the baseline would be an increase of concern



Baseline Comparator for Responders to DAAs?

For the majority whose enzymes return to normal on treatment, if followed by a rise in the ALT levels, assessment for possible liver or viral breakthrough can no longer be measured against the baseline level, since ALT levels may have declined in response to treatment

A subsequent increased ALT value should therefore be compared with the new on-treatment level of ALT, concern being raised if the increase exceeds 2-3 fold



Assessing Dili in Clinical Practice Differs from that of Clinical Trials

In clinical trials, if there is concern for possible developing dili, all the elements required to perform causality assessment are available, namely pre-treatment and baseline chemistries and repeated on-treatment ALT measurements

In clinical practice, however, dili is suspected only when a person receiving recent treatment develops symptoms, such as fever, fatigue, or nausea, or is jaundiced, and screening reveals increased serum enzymes with or without hyperbilirubinemia

In most instances, there are no baseline or on-treatment pre-illness values to serve as comparators; also, unlike the clinical trial, the actual onset of liver injury may not be identifiable



Assessing Dili in Clinical Practice

In the absence of baseline and on-treatment chemistries, the criteria used for triggering concern for possible impending dili in clinical trials cannot be applied in clinical practice

In clinical practice, the presence of relevant symptoms and/or jaundice is the reason for performing serum enzyme testing, so that identifying raised ALT values simply confirms the existence of liver disease rather than acting as a dili signal

Thereafter, extensive screening for cause is undertaken followed by careful causality assessment using careful clinical judgment or standardized instruments such as RUCAM



Conclusion

The lack of a definitive biomarker for dili places the burden on screening for possible emerging dili on the ALT value

There is presently limited consensus on how best to apply the ALT for this purpose

Greater consistency in setting the parameters of its applicability is needed until it is replaced by better means of detecting incipient dili

The approach to screening for dili differs depending upon whether it occurs during clinical trials or in clinical practice