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The Adaptive Response (Drug Tolerance) Helps to Prevent Drug-Induced Liver Injury



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G&H How frequently do drugs cause elevations in liver-associated enzymes or lead to drug-induced liver injury?

JHL Elevations in liver-associated enzymes (LAEs)—in particular, alanine aminotransferase (ALT) and aspartate aminotransferase—are seen fairly frequently in clinical practice and can be related to any number of acute and chronic causes, including viral hepatitis, fatty-liver disease, alcohol, a variety of autoimmune and metabolic disorders, and several drugs. When it comes to abnormal liver test results and drug-induced liver injury (DILI), it is important for clinicians to draw a distinction between asymptomatic, low-level elevations in LAEs and biochemical changes that may be indicative of more serious hepatic damage. Although reliance on ALT as a marker of liver injury is imprecise and only indicates that some type of hepatocellular injury has occurred, ALT nonetheless remains the most widely employed biochemical tool for recognizing DILI.

The terms “drug tolerance” and “adaptive response” synonymously refer to the phenomenon in which a drug induces mild elevations in ALT or other LAEs that either do not progress beyond the asymptomatic, low-level range or return to normal (or baseline) despite continuation of the medication. Importantly, these elevations are asymptomatic and are not associated with any clinical or biochemical evidence of functional hepatic impairment, such as a concomitant rise in serum bilirubin level or international normalized ratio.

Minor asymptomatic elevations of LAEs tend to occur more frequently with certain drug classes. Statins and antimicrobial drugs are among the most common

agents associated with drug tolerance. Up to 5% of patients taking statins will develop ALT elevations, which usually remain less than 3 times the upper limit of normal (ULN) and are not associated with any hepatic-related symptoms. Nevertheless, owing to the labeling that accompanied statin approval, which mentioned a risk of hepatotoxicity and need for LAE monitoring, even such low-level elevations continue to cause consternation in the clinical setting, and the drug is often stopped prior to determining if tolerance will develop.

Other drugs are associated with a prevalence of sub-clinical hepatic enzyme elevations in the 10–20% range, including a number of antibiotics, such as erythromycin estolate, ketoconazole, and isoniazid. Agents associated with a higher prevalence of drug tolerance (up to 25%) include chlorpromazine, amiodarone, nicotinic acid, phenytoin, valproate, and 6-mercaptopurine. An example of a drug that can cause extreme elevations in ALT is tacrine (Cognex), which was previously used to treat Alzheimer disease. Upward of 50% of patients taking this medication developed elevations in ALT levels, sometimes as high as 20 times the ULN. In nearly all cases, these enzyme levels did not progress further and came down toward normal (sometimes after halting the medication temporarily), and patients were able to restart the medication without recurrent problems.

G&H Can drugs causing tolerance ever be associated with more severe liver injury?

JHL Fortunately, severe DILI in the United States is relatively uncommon, as most drugs are safe with respect

to the liver. Nevertheless, nearly all of the drugs that have been reported to cause subclinical ALT elevations are capable of causing more severe hepatotoxicity. The frequency with which DILI occurs is usually quite low. In the case of statins, only about 1% of patients will have ALT values that exceed 3 times the ULN, and symptomatic hepatitis is unusual. A similarly low frequency of symptomatic LAE elevations is seen with amiodarone. Isoniazid leads to overt liver injury in 1–4% of cases and is usually age-related. Overall, symptomatic liver injury occurs in just a fraction of patients who develop lower-level ALT elevations.

The most feared form of acute DILI is acute liver failure (ALF). There are estimated to be 2,000–2,500 ALF cases of all causes annually in the United States, based on estimates from various registries, including the US Acute Liver Failure Study Group. Approximately 40–50% of these cases are due to intentional or inadvertent overdoses with acetaminophen. Among the remainder, only about 12% of ALF cases are due to all other drugs, including herbal therapies and other supplements. From the point of view of absolute numbers, this percentage represents only 250–300 instances of ALF from these other agents. Acute viral hepatitis accounts for approximately the same number of cases of ALF per year in the United States.

With respect to specific drugs causing ALF, isoniazid leads the list, with about 50 cases per year. ALF from statins, while reported anecdotally, appears to be extremely rare, on the order of 1 case per million users. This frequency is not dissimilar to the background rate of ALF in the United States, which occurs without any specific cause.

G&H At what point should elevations in liver enzyme levels prompt discontinuation of a drug?

JHL Despite the low frequency of ALF seen with most drugs, it is important to recognize that a small percentage of patients in whom LAEs begin to rise can go on to develop progressive injury and even ALF. Patients taking such agents, in whom ALF is a recognized consequence of treatment, generally need to be monitored more closely. To prevent ALF from developing, clinicians must be vigilant when treating such patients and monitor not only the biochemical levels of ALT and bilirubin, but also pay attention to the development of symptoms of hepatitis, such as loss of appetite, malaise, fatigue, nausea, abdominal pain, and jaundice. If any of these symptoms develop, the medication must be stopped at that point. While the adaptive response is thought to prevent injury in the majority of patients, clinicians need to be aware that certain patients may cross a threshold after which liver injury is no longer reversible when the medication is discontinued.

US Food and Drug Administration (FDA) guidance in the arena of preventing drug-induced hepatotoxicity has been quite helpful. The stopping rules that have been put into place for new drugs under development can also be used by clinicians who prescribe existing medications. These recommendations suggest that if a patient's ALT level rises above 3 times the ULN but is not associated with any symptoms or evidence of hepatic impairment, such as a rise in bilirubin, the drug can likely be continued safely with periodic enzyme monitoring. For ALT rises above 5 times the ULN, more intensive monitoring should be performed, and if the ALT rises above 8 times the ULN, clinicians should consider stopping the drug at that time. If there are no alternatives to the drug being used, in some cases the drug may be restarted once the patient's ALT level returns toward normal.

Although the exact level of ALT elevation that signals the risk for the development of ALF is not known with any certainty, an 8-fold rise from a normal baseline is generally felt to represent the threshold below which DILI is still considered to be reversible for most drugs causing hepatocellular injury. However, for any patient who develops a rise in ALT above 3 times the ULN in association with a total serum bilirubin level greater than twice the ULN (implying impaired liver function from the injury) or any hepatic-related symptoms, the FDA guidance states that Hy's Law criteria have been met, which implies that the patient is at increased risk for developing ALF. Hy's Law, named for the clinical observation made by the late Hyman Zimmerman, predicts that patients who develop drug-induced hepatocellular jaundice have a mortality rate that can exceed 10%. In terms of specific drugs, the mortality rate associated with isoniazid was 10–20%, and anticonvulsant drugs such as phenytoin had mortality rates of up to 50% in the pre-liver transplantation era. This rule continues to be used by the FDA as well as drug developers, and it calls for enhanced vigilance on the part of all clinicians when invoked.

G&H What is the mechanism by which elevated LAEs normalize in some patients?

JHL This is the key question when we are dealing with what appears to be an adaptive response or drug tolerance. Although mild ALT elevations are assumed to represent some form of subclinical hepatocellular injury, the fact that these enzymes fail to progress further and are not associated with any hepatitis-related symptoms indicates that reparative or other protective processes are at work, which prevent more serious injury from occurring. Very little information is available concerning any histologic correlates of drug tolerance in such patients. Liver biopsies are rarely, if ever, performed in patients who develop mild

asymptomatic rises in LAEs. Similarly, limited data can be gleaned from animal toxicology studies, which generally do not perform liver biopsies for only trivial elevations in ALT or other LAEs. What is known from studying well-established hepatotoxic agents such as acetaminophen is that a number of protective cytokines and chemokines appear to be upregulated to counter the effects of injurious factors released in response to the formation of reactive oxygen species or other causes of intracellular stress that activate mechanisms leading to drug injury. Elegant work to date concerning this anti-inflammatory cascade suggests that interleukin-6 and interleukin-10, among other protective proteins, combat the proinflammatory effects of interferon- γ , fas-ligand, and tumor necrosis factors, which if unregulated, would likely lead to a more severe inflammatory response and cell death.

Exactly how the events leading to drug tolerance relate to a patient's innate or adaptive immune response is a matter of ongoing study. Various host factors have been cited to predict the likelihood of DILI. In general, women are more likely than men to develop liver injury, and adults are more susceptible than children. Also, individuals who drink alcohol might be predisposed to adverse reactions with some agents, and obesity may predispose patients to certain drug-induced hepatic reactions. However, the genetic make-up of the host very likely underlies the balance between injurious and protective pathways. A number of genetic polymorphisms have been proposed as potential biomarkers to identify patients at risk of certain drug injury. A recent example is *HLA-B*5701*, testing for which is recommended in patients receiving abacavir (Ziagen, ViiV Healthcare) as part of an HIV treatment regimen. Patients who harbor that particular phenotype are at much higher risk of developing hypersensitivity reactions to the drug (which may involve DILI), and this drug is generally avoided in such individuals. Similar *HLA* polymorphisms have been identified for patients at risk of DILI from amoxicillin, flucloxacillin, and other antibiotics. The role of other genetic polymorphisms for predicting isoniazid-induced DILI also has been intensively studied. For most other drugs, however, we lack an accurate biomarker that would predict who is at risk of developing severe hepatic injury.

G&H Why do clinicians need to know about this adaptive response?

JHL An understanding of drug tolerance is extremely important because this phenomenon allows many drugs to be continued safely despite minor elevations in LAEs such as ALT. If clinicians know that such low-level enzyme elevations are not likely to continue to rise progressively, then the patient can benefit from remaining on that

drug. This is especially true in the case of statins, where even today, many prescribers are quite concerned when patients develop even these low-level enzyme elevations. In many instances, the statin is stopped in the face of such abnormalities, often despite the fact that the drug may have been taken without incident for years.

It is important to note that the usual time frame in which enzymes first rise and an adaptive response takes root is generally within the first 12 weeks after starting a new drug. This timeframe may reflect the postulated mechanism of injury for most drugs that do not act via a hypersensitivity or immunoallergic reaction (in which case, acute DILI often announces itself within days or weeks of exposure with typical symptoms of a fever, rash, or eosinophilia). When such a reaction occurs, it is most prudent to discontinue the offending agent, whether or not LAE elevations are part of the event. For the majority of drugs causing DILI that act through the possible formation of a reactive metabolite, it becomes less likely that serious hepatic injury would develop *de novo* after 6 months, and it is decidedly rare that any drug would be associated with acute injury after more than 1 year of continued use. Patients who have been on statins for a number of years who are found to have elevated liver enzyme levels after such a duration are often discontinued from the statin at that time, even though it is unlikely to have been the cause of the liver enzyme elevation. Patients on statins can have heart disease, gallbladder disease, and many other comorbidities that affect such users, and it is important that the clinician be able to perform an adequate causality assessment before blaming a particular agent for an underlying illness.

It is somewhat ironic that concern about statin-related liver injury still remains a major source of consultation in hepatology practices, given the increasing information demonstrating that statins are more likely to be hepatoprotective than they are hepatotoxic. There are now numerous examples of patients with chronic hepatitis B or C virus infection who have improved responses to antiviral treatment when taking a statin. In addition, patients with underlying fatty-liver disease from nonalcoholic steatohepatitis have long been shown to be able to safely receive statins, even in the face of mildly elevated liver enzyme levels. Randomized controlled prospective trials show that patients receiving statins actually have fewer instances of hepatic events than patients not receiving statins. Such information is now reflected in new labeling from the FDA stating that patients with no sign of liver disease who are starting statins no longer need to have routine liver enzyme monitoring; this revision is an acknowledgment of the rarity of severe DILI from statins and suggests that much of our previous concern may have been unfounded.

G&H What are the most important take-home messages for clinicians who may be concerned about elevations in LAEs?

JHL For the present, the importance of stopping rules such as Hy's Law suggests that if the drug is discontinued before a patient crosses the threshold of hepatotoxic irreversibility, then ALF can be prevented. As noted above, there are relatively few drugs that are reported to cause ALF with any regularity, including isoniazid, other antituberculosis medications, and a number of anticonvulsant agents. Some herbal medications, the antithyroid agent propylthiouracil, and other drugs are also part of this list. However, the vast majority of agents can be used quite safely, even though they may be associated with mild asymptomatic elevations in LAEs, owing to the hepatoprotective events that develop as a result of the drug tolerance adaptive response. This effect is particularly important in the case of statins. Knowing the threshold between an adaptive response and the development of ALF is crucial when it comes to prescribing potentially hepatotoxic medications.

Moving forward, the ultimate goal will be to develop biomarkers or genetic analyses that can accurately predict who is at risk for severe hepatic injury prior to the drug being taken. In that way, we should be able to prevent most instances of non-acetaminophen-related ALF in the future, lessen the need for frequent liver enzyme monitor-

ing for many agents, and permit clinicians to administer a desired drug with greater confidence by diminishing the concerns that arise due to elevations in LAEs.

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