ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Drug-Induced Liver Injury

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G&H What are the different types of drug-induced liver injury?

NC Drug-induced liver injury can be divided into direct hepatotoxicity and idiosyncratic drug-induced liver injury. Direct hepatotoxicity will develop in a predictable fashion if high enough doses of a drug are given. A classic example is the liver damage that can result in any patient who takes very high doses of acetaminophen. Idiosyncratic drug-induced liver injury refers to the reaction that can occur in a very rare and unpredictable and generally dose-independent fashion.

> Approximately 50% of acute idiosyncratic drug-induced liver injury cases seen in the United States are attributed to antibiotics, antituberculosis agents, and antifungals.

G&H Which types of drugs most commonly cause idiosyncratic drug-induced liver injury?

NC Antimicrobials are the largest group of offending drugs. Approximately 50% of acute idiosyncratic drug-induced liver injury cases seen in the United States are attributed to antibiotics, antituberculosis agents, and antifungals. Idiosyncratic drug-induced liver injury due to herbal and dietary supplements is growing in its occurrence, and as many as 20% of idiosyncratic drug-induced liver injury cases are due to such agents. Supplements commonly associated with idiosyncratic drug-induced liver injury are anabolic steroids and weight loss supplements such as Herbalife and OxyElite Pro products. Other offending agents include anticonvulsants and cardiovascular compounds.

G&H Is there a resource for clinicians to check whether a particular medication is associated with liver injury?

NC Over the past decade, Dr Jay Hoofnagle, under the auspices of the National Institutes of Health and the National Library of Medicine, has developed a comprehensive and unbiased web-based resource, LiverTox (https://livertox.nih.gov), which provides up-to-date, accurate, and easily accessible information on idiosyncratic drug-induced liver injury. I find this site to be an incredible resource for my clinical colleagues and myself.

G&H When liver injury is caused by a drug, how severe does it tend to be?

NC Most idiosyncratic drug-induced liver injury is mild, but acute liver failure can occur on rare occasions. Approximately 50% to 60% of patients with idiosyncratic drug-induced liver injury are asymptomatic and have

silent increases in liver biochemistries, approximately 30% of patients have jaundice, and the remainder have severe liver injury.

G&H What are the possible mechanisms behind idiosyncratic drug-induced liver injury?

NC One possibility is the reactive metabolite theory. When a compound is metabolized in the liver, some of its metabolites are reactive and toxic, resulting in liver injury. Another theory involves immune-mediated mechanisms whereby the compound or metabolite generates an immune response, which causes damage to the liver. There is not a lot that is understood about the mechanisms of idiosyncratic drug-induced liver injury.

G&H Are there any risk factors associated with idiosyncratic drug-induced liver injury?

NC It appears that there are several compound- and host-specific risk factors. One compound-specific risk factor is a high daily dose. For example, an antibiotic that is taken at 1 g per day may have a higher risk of idiosyncratic drug-induced liver injury than a drug taken at 50 mg per day. In addition, the risk of idiosyncratic drug-induced liver injury may be associated with the chemical characteristics of the compound (eg, whether it is lipophilic and how it is metabolized).

Host-specific risk factors can include genetic factors. For example, certain human leukocyte antigen genetic variants pose risk for idiosyncratic drug-induced liver injury with select medications, such as amoxicillin/clavulanate, minocycline, and trimethoprim/sulfamethoxazole. For certain compounds, such as antituberculosis agents, heavy drinking can be a risk factor for idiosyncratic drug-induced liver injury, as can underlying hepatitis B or C virus infection with HIV medications. Race may also play a role. A recent study found that African Americans may be susceptible to developing liver injury from some compounds (eg, trimethoprim/sulfamethoxazole) and may have worse outcomes when it occurs.

In addition, some researchers believe that patients may be at higher risk for idiosyncratic drug-induced liver injury if they have comorbidities such as underlying chronic liver disease. However, other researchers believe that underlying liver disease does not necessarily increase the risk for idiosyncratic drug-induced liver injury; the comorbidity would just worsen the patient's outcomes if the liver injury were to occur.

G&H Currently, how can doctors determine whether liver damage is the result of a drug or another cause?

NC Diagnosis is based on the occurrence of liver injury with exposure to a new medication or supplement in the absence of a competing etiology. In other words, a patient starts a new medication and then develops liver injury with or without symptoms within weeks. However, it is essential to rule out competing etiologies for the liver injury. Just because a patient takes a new drug and develops jaundice does not mean that the drug was the cause; acute liver injury can have other causes, such as acute viral hepatitis, autoimmune liver disease, or heart failure.

G&H What are the challenges associated with developing biomarkers for the diagnosis or prognosis of idiosyncratic drug-induced liver injury?

NC A major challenge is the rarity of the event; idiosyncratic drug-induced liver injury generally occurs only in approximately 1 in 10,000 individuals. In addition, a number of these liver injury cases are asymptomatic. All of this makes it difficult to develop and validate biomarkers. Currently, there is no gold standard diagnostic test for idiosyncratic drug-induced liver injury; the condition is presently a diagnosis of exclusion in appropriate patients, as discussed above. However, research is presently underway on the development of biomarkers for diagnosing or prognosticating idiosyncratic drug-induced liver injury.

G&H Which biomarkers have been examined thus far?

NC Preliminary findings from a study by Dr Rachel J. Church and colleagues were released online in January 2018 ahead of print publication in *Hepatology*. The researchers, of which I was a part, identified several promising biomarkers: microRNA-122, glutamate dehydrogenase (GLDH), total cytokeratin 18 (K18), osteopontin, and macrophage colony-stimulating factor receptor (MCSFR). GLDH and microRNA-122 are being examined for diagnosis, whereas K18, osteopontin, and MCSFR are being studied for prognosis. However, all of these biomarkers need to undergo testing as well as validation before they can be used in clinical practice.

G&H How do these biomarkers differ?

NC They are based on different mechanisms, such as necrosis or apoptosis. For example, some involve cell injury, and others involve leakage of cellular enzymes or microRNA.

G&H Has there been other research on any of these biomarkers?

NC There has also been some interest in identifying biomarkers for drug-induced hepatic steatosis. K18 appears to be the most promising biomarker. However, in general, there is not yet extensive biomarker research in idiosyncratic drug-induced liver injury because of the challenges previously discussed.

G&H Are there any studies currently underway on biomarkers in this area?

NC There is a biomarker initiative in Europe in which idiosyncratic drug-induced liver injury is one of the top phenotypes being studied. In addition, the US Drug-Induced Liver Injury Network, of which I am a part, is currently conducting a substudy to focus on biomarkers.

G&H In a patient with idiosyncratic drug-induced liver injury, at what point is drug discontinuation necessary?

NC The drug should be stopped immediately if a patient has suspected idiosyncratic drug-induced liver injury with jaundice or liver function test results (eg, alanine aminotransferase or alkaline phosphatase) that are getting progressively worse. In addition, drug discontinuation is necessary with suspected idiosyncratic drug-induced liver injury that is associated with symptoms such as severe nausea, abdominal pain, or skin rash.

G&H Is the liver injury usually reversible once the drug is stopped?

NC Yes, the liver injury is usually reversible, although it depends on how bad the injury is. However, once the patient develops severe jaundice, the prognosis becomes worse. At that point, doctors can generally only stop the offending drug and provide supportive care. Occasionally, corticosteroids may be administered, but there have been no controlled studies to test their effectiveness in this setting.

G&H If the liver injury is reversed, can the drug be rechallenged eventually?

NC Rechallenge is not recommended unless the medication is essential for managing the patient's health. This situation is generally encountered in cancer chemotherapy; patients need the drug, so it is restarted at a lower dose with careful monitoring and after patients are informed of the risks.

G&H What are the next steps in research?

NC Research is needed to try to understand the mechanisms for idiosyncratic drug-induced liver injury, particularly involving its genetic basis. As previously mentioned, there is some research underway on diagnostic and prognostic biomarkers. Finally, my colleagues and I, as well as investigators from Europe and Asia, are trying to develop a treatment that can be given to patients with severe idiosyncratic drug-induced liver injury.

Dr Chalasani has consulting agreements and research grants from several pharmaceutical companies, but none are directly or significantly related to the contents of this column.

Suggested Reading

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